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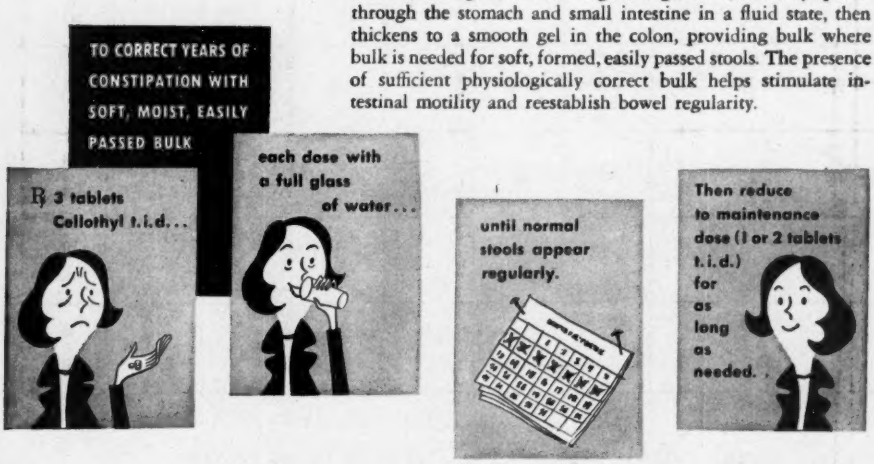
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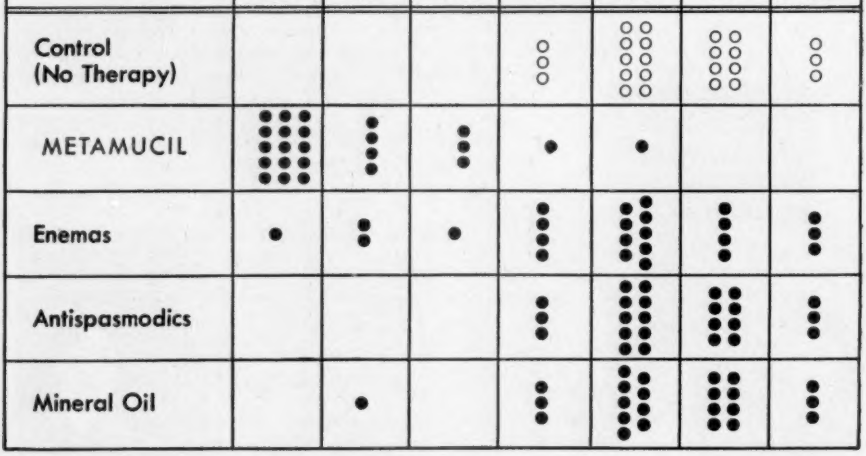

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*Barowsky, H.: A Roentgenographic Evaluation of the Common Measures Employed in the Treatment of Colonic Stasis, Scientific Exhibit, National Gastroenterological Association, Chicago, Sept. 17-22, 1951.

RESEARCH IN THE SERVICE OF MEDICINE **SEARLE**

CONTENTS

PAGE

Clinical Use of Fat Injected Intravenously. THEODORE B. VAN ITALLIE, M.D.; WILLIAM R. WADDELL, M.D.; ROBERT P. GEYER, PH.D., AND FREDRICK J. STARE, PH.D., M.D., BOSTON 353

Mesenchymal Tumors of the Stomach. GLADDEN V. ELLIOTT, M.D., AND HUGH M. WILSON, M.D., ST. LOUIS 358

Treatment of Thyrotoxicosis with 1-Methyl-2-Mercaptoimidazole. R. L. KENDRICK, M.D., ROCHESTER, MINN.; KENT BALLS, M.D., AND EDWARD ROSE, M.D., PHILADELPHIA 368

Studies on Streptococcal Hyaluronidase and Antihyaluronidase. JOSEPH M. DI CAPRIO, M.D.; LOWELL A. RANTZ, M.D., AND ELIZABETH RANDALL, M.A., SAN FRANCISCO 374

Further Observations on the Use of Triethylene Melamine in Neoplastic Diseases. JANE C. WRIGHT, M.D.; AARON PRIGOT, M.D.; LOUIS T. WRIGHT, M.D., AND ISIDORE ARONS, M.D., NEW YORK 387

Klebsiella Pneumoniae Meningitis: Review of the Literature and Report of a Case with Bacteremia and Pneumonia, with Recovery. ALVIN J. THOMPSON, M.D.; EDWARD B. WILLIAMS JR., M.D.; EDWIN D. WILLIAMS, M.D., AND JOHN M. ANDERSON, B.S., ST. LOUIS 405

Further Studies on the Relationship of S_f 10-20 Lipoprotein Molecules to Atherosclerosis. THOMAS P. LYON, M.D.; HARDIN B. JONES, PH.D.; DEAN M. GRAHAM, B.S.; JOHN W. GOFMAN, M.D.; FRANK T. LINDGREN, AND A. YANKLEY, M.D., BERKELEY, CALIF. 421

CASE REPORTS:

Bacillary Dysentery Due to Shigella Alkalescens. JOSEPH FELSEN, M.D., AND WILLIAM WOLARSKY, M.D., NEW YORK 428

Acute Hemolytic Anemia Associated with Myeloid Metaplasia of the Spleen: Report of a Case Treated by a Splenectomy. MAURICE A. CLAMAN, M.D., AND WILLIAM J. COLLIER, M.D., WADSWORTH, KAN. 431

Primary Carcinoma of the Liver. HAROLD J. SCHUPBACH JR., M.D., AND RAID B. CHAPPELL, M.D., MEMPHIS 436

Syndrome of Joint and Cartilaginous Pathologic Changes with Destructive Iridocyclitis: Comparison with Described Concurrent Eye and Joint Diseases. A. C. HILDING, M.D., PH.D., DULUTH, MINN. 445

Primary Carcinoma of the Trachea. HAROLD ZAROWITZ, M.D., AND JULIAN B. HOFFMAN, M.D., NEW YORK 454

PROGRESS IN INTERNAL MEDICINE:

Syphilis: A Review of the Recent Literature (Concluded). HERMAN BEERMAN, M.D.; WILLIAM T. FORD, M.D.; LESLIE NICHOLAS, M.D., PHILADELPHIA, AND LAWRENCE KATZENSTEIN, M.D., WILMINGTON, DEL., WITH THE COLLABORATION OF FRANK W. REYNOLDS, M.D., AND T. GUTHE, M.D., GENEVA, SWITZERLAND 464

NEWS AND COMMENT 520

BOOK REVIEWS 522

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CLINICAL USE OF FAT INJECTED INTRAVENOUSLY

THEODORE B. VAN ITALLIE, M.D.
WILLIAM R. WADDELL, M.D.
ROBERT P. GEYER, Ph.D.
AND
FREDRICK J. STARE, Ph.D., M.D.
BOSTON

A MAJOR problem in parenteral feeding is associated with the need for a nonsclerosing preparation for intravenous administration which contains a large supply of calories in a small volume of fluid. Fat emulsions appear to offer a solution to this problem. Fat particles do not exert an osmotic effect; accordingly, fat may be injected in high concentrations without damage to veins and in a relatively small fluid volume. Unlike dextrose and amino acids, fat is not excreted in the urine in significant amounts.

Among the earliest clinical studies involving the intravenous administration of fat emulsions for caloric purposes was one reported by Yamakawa in Japan in 1920.[1] Later, in this country, Holt, Tidwell, and Scott [2] studied the effect of intravenous fat administration in experimental animals and in children.

In the interim, although fat emulsions for intravenous administration still have not become available commercially, their use in man is no longer a novelty. Difficulties in manufacture, storage, and transport of these fat preparations have prevented unrestricted use of the material. However, in several laboratories [3] it has been possible to prepare fat emulsions suitable for intravenous use in patients. In recent months we have given fat emulsions intravenously to 35 patients in whom

Read before the Section on Experimental Medicine and Therapeutics at the One-Hundredth Annual Session of the American Medical Association, Atlantic City, June 13, 1951.

From the Department of Nutrition, Harvard School of Public Health, the Medical and Surgical Clinics, Peter Bent Brigham Hospital, and the Surgical Service, Massachusetts General Hospital.

This study was supported in part by Grants-in-Aid from the Upjohn Company, Kalamazoo 99, Mich.; the Nutrition Foundation, New York; the Cancer Research Grants Branch, National Cancer Institute, Bethesda, Md.; Armour & Company, Chicago, and under contract with the United States Army Research and Development Board of the Surgeon General's Office, Washington, D. C.

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2. Holt, L. E., Jr.; Tidwell, H. C., and Scott, T. F.: The Intravenous Administration of Fat: A Practical Therapeutic Procedure, J. Pediat. **6**:151 (Feb.) 1935.

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neither pyrogenic nor other untoward responses were observed. Fifteen of the 35 received 5 to 36 separate infusions; each of them had at least 500 cc., and several received as much as 2,000 cc. at one time. The preparations contained fat in concentrations of 10, 12.5, and 15%, providing respectively 1,100, 1,325, and 1,600 calories per liter. Our experience with these patients constitutes the basis of this report (Table).

The fat emulsions were prepared by methods already described.[4] They are made by a homogenization process, utilizing a phosphatide stabilizer and a co-stabilizer in low concentrations. The resulting preparation contains particles averaging less than 1μ in diameter and is stable to autoclaving.

Metabolic, hematologic, chemical, and pathologic studies on the intravenous administration of fat emulsions to animals have been reported.[5] In essence, these studies show that suitably prepared fat emulsions administered intravenously are rapidly metabolized, "spare" nitrogen, and are nontoxic. Preliminary clinical

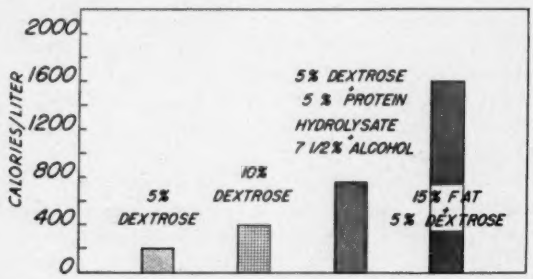

Fig. 1.—Comparison of caloric values per liter of various solutions for parenteral administration.

Caloric Role of Intravenously Administered Fat in Nutritional Management of a Representative Group of Patients Requiring Parenteral Alimentation

Age	Sex	Diagnosis	Daily Fat Infusions	Calories/Day from Fat Given Intravenously
17	♀	Ulcerative colitis	14	1,100
46	♂	Chronic peritonitis	36	1,170
66	♀	Carcinoma of stomach	11	1,325
55	♀	Nontropical sprue	14	663
35	♀	Carcinoma of cervix	14	1,100
45	♂	Carcinoma of pancreas	14	1,600
29	♂	Idiopathic steatorrhea	9	1,325

4. Geyer, R. P.; Mann, G. V., and Stare, F. J.: Parenteral Nutrition: IV. Improved Techniques for the Preparation of Fat Emulsions for Intravenous Nutrition, J. Lab. & Clin. Med. **33**:153 (Feb.) 1948.

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studies on the intravenous use of fat emulsions have supported the findings in animals.[6]

The role of fat given intravenously in parenteral nutrition is to provide calories. By means of dextrose and protein hydrolysates given by vein, it is possible to realize the body's needs for carbohydrate and protein. However, it never has been practicable to meet energy requirements solely by parenteral feeding. In this regard, it is not uncommon to see patients who are unable to take or to absorb adequate amounts of food become increasingly depleted, despite liberal parenteral administration of solutions of sugar and amino acids.

An inadequate caloric intake for a short time is not necessarily harmful to the patient who is acutely ill. However, during prolonged periods of energy deficit, body protein is broken down to supply calories and essential carbohydrate. A variable supply of calories is made available from depot fat. Yet, in the usual patient, calories from fat stores are by no means an adequate supplement to dextrose and amino acids administered parenterally. And in the chronically ill patient reserves of fat are at a minimum. In parenteral nutrition there is no substitute for an adequate supply of calories.[7]

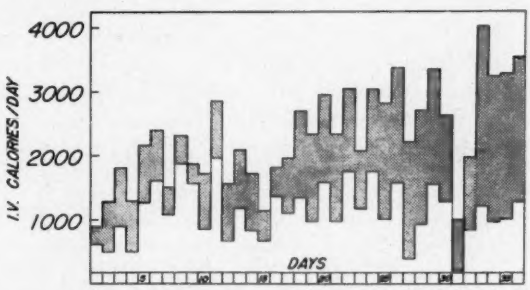

Fig. 2.—Intravenous caloric intake of D. M., a 46-year-old man, with chronic intestinal obstruction requiring total parenteral nutrition. Caloric contribution of fat emulsion given intravenously is indicated by cross hatching. Areas beneath cross hatching represent calories from intravenously given dextrose, alcohol, and amino acid solutions.

CLINICAL USES

The clinical uses of fat injected intravenously are manifold and may be inferred from its caloric properties. If total parenteral feeding is needed for a prolonged period, a patient's survival may depend directly upon the number of calories that can be administered to him. In a situation of this kind, fat given intravenously may play a decisive role. The following case report illustrates this:

D. M. was a 46-year-old mechanic who was brought into the emergency ward in a condition of shock and dehydration. Three days previously he had experienced a sudden sharp pain in the right abdomen. As the pain gradually subsided, it was replaced by nausea, vomiting, and diarrhea. The following day he began to experience severe pain in both shoulders. The symptoms persisted; he grew increasingly weak and finally sought admission to the hospital.

6. Neptune, E. M., Jr.; Geyer, R. P.; Saslaw, I. M., and Stare, F. J.: Parenteral Nutrition: XII. The Successful Intravenous Administration of Large Quantities of Fat Emulsion to Man, Surg., Gynec. & Obst. **92**:365 (March) 1951.

7. Moore, F. D.: Adaptation of Supportive Treatment to Needs of the Surgical Patient, J. A. M. A. **141**:646 (Nov. 5) 1949.

At the time of entry the patient was in profound shock and showed signs of generalized peritonitis. A diagnosis of perforated viscus was made. He responded to supportive therapy, and over the course of the next few weeks the peritoneal infection localized, forming pelvic, subhepatic, and right lower quadrant abscesses. These were drained, but the condition of the patient remained critical, owing largely to persistent complete intestinal obstruction which prevented any oral intake whatever. Constant intubation was necessary, and throughout this period the patient was fed entirely by vein.

Alcohol, dextrose, and protein hydrolysates were administered in liberal amounts; nevertheless, the patient became increasingly cachectic. After 31 days fat emulsions for intravenous use became available as an additional source of calories. For 36 days thereafter he was continued on total intravenous feeding, but in addition to the conventional nutrients he was given 36 infusions of fat emulsion, which provided a total of 42,214 calories. During the period of supplementation with fat given intravenously, the caloric intake from sources other than fat totaled 39,598 calories, an average of 1,100 calories per day. Fat emulsions provided an average of 1,173 calories per day (Fig. 2).

After 67 days of complete parenteral nutrition, the patient began to retain small amounts of food. Parenteral feeding was discontinued, and his intake by mouth soon reached adequate levels. Ten days later the patient was convalescing satisfactorily.

COMMENT

It is difficult to believe that this patient could have survived his illness without the aid of the calories supplied to him by the intravenously administered fat. Yet the indications for intravenous alimentation with fat are not necessarily so extreme. Fat emulsions for intravenous administration can be given as a caloric supplement to patients who are either unwilling or unable to take an adequate diet. They can be used to help prepare depleted patients for operations and also to accelerate convalescence after surgical treatment. In anorexias associated with acute and chronic illnesses of all kinds, fat given intravenously can help maintain the patient's caloric intake at a high level.

The technique for the administration of fat emulsions is similar to that employed in the intravenous administration of other solutions. A liter of fat providing 1,600 calories can be given in 120 minutes or less. Clearance of fat from the blood stream usually is complete after four or five hours. Patients receiving fat intravenously have never shown clinical evidence of ketosis during or after fat administration, and among the hundreds of patients who have received fat intravenously from us there never has been a fatality attributable to the preparation. Preliminary studies of red-cell fragility after fat administration have failed to show changes in integrity of the red-cell membrane. Liver-function tests done on patients after completion of prolonged parenteral feeding with fat have, so far, failed to disclose evidence of liver damage due to the fat preparation. Liver biopsy studies and studies on the effect of fat emulsions on blood lipids and lipoproteins are in progress, but insufficient data have accumulated to justify a report at this time.

Untoward effects occasionally have been associated with the intravenous administration of fat. The commonest one has been a febrile response to the fat. Certain batches of fat for intravenous administration have proved to be pyrogenic, others nonpyrogenic. Patients reacting with a chill and a fever to one preparation have shown no untoward response to a similar preparation containing oil from a different lot. We have found no evidence to suggest that the febrile response to fat is a result of the production, from fat oxidation, of uncompensated metabolic heat.

A second and rare untoward response has been nausea, followed occasionally by transient vomiting. This may occur during or after intravenous administration of fat. Other side-effects which have been observed from time to time have included transient flushing of the face and neck and moderate fluctuations in blood pressure. Apparently tachyphylaxis occurs after a small amount of the preparation has been administered, and the vasomotor reactions do not recur with early further administration of the fat emulsion. It is believed that most of the untoward effects described are due to occasional impurities either in the stabilizing system or in the fat itself, and that they are not intrinsic to fat administered intravenously.

SUMMARY AND CONCLUSIONS

Fat emulsions for intravenous use make possible the convenient administration of a large supply of calories in a small volume of fluid. Such emulsions are nontraumatic to veins, and virtually no portion of their content of fat is excreted in the urine or in the feces.

The successful clinical use of fat emulsions for intravenous administration is an established fact. As much as 2 liters of fat emulsion, providing 3,200 calories, has been given to patients in a 12-hour period without untoward response. One patient received fat intravenously for 36 days, and this furnished a total of 42,214 calories. It is believed that the calories from the infused fat made possible his survival.

No evidence of damage to the liver or of disturbance in the integrity of the red-cell membrane has been found in preliminary studies directed toward these problems.

In the light of the information available concerning the clinical administration of fat intravenously, it is felt that discussions which center around the feasibility of administration of fat to patients are beside the point. Attention might better be directed to the problems associated with the producion of a consistently nonpyrogenic preparation which will remain stable despite changes in environmental temperature and rough handling. When these problems have been solved, a new era in parenteral feeding will have begun.

Dr. Francis D. Moore, Professor of Surgery, Harvard Medical School, and Surgeon-in-Chief, Peter Bent Brigham Hospital, cooperated in this work.

MESENCHYMAL TUMORS OF THE STOMACH

GLADDEN V. ELLIOTT, M.D.
AND
HUGH M. WILSON, M.D.
ST. LOUIS

DURING the past eighteen months our interest in nonepithelial tumors of the stomach has been stimulated by the appearance of a relatively large number of such lesions. Although the mesenchymal group of neoplasms consists of lymphosarcomas, leiomyomas, leiomyosarcomas, fibromas, neurofibromas, and lipomas, the lymphosarcomas and leiomyomas are by far the most important in both frequency and clinical significance.

It has been estimated by various authors [1] that sarcomas constitute only 1 to 2% of all gastric neoplasms. Our unusual experience is illustrated by the fact that lymphosarcomas have accounted for 14.3% of all gastric neoplasms found in a total of 5,183 examinations of the stomach made during the past 18 months.

During the same period, we have discovered five clinically significant leiomyomas of the stomach—representing an additional 4.2% of all gastric neoplasms. Although this figure agrees more closely with that reported elsewhere,[2] many of the previous reports are based on autopsy observations and are misleading, since many of the tumors found in such circumstances are small and undoubtedly of no clinical significance.

LEIOMYOMAS

A. *Clinical Findings.*—The clinical findings presented by our group of five leiomyomas plus one subserosal lipoma of the stomach are summarized in Table 1. The patients' ages ranged from 13 to 65 years and the duration of symptoms from three months to two years.

The frequency of hemorrhage has been previously emphasized by Sahler and Hampton,[3] of the Massachusetts General Hospital, Boston, and Golden and Stout,[4]

From the Department of Radiology, Washington University School of Medicine.

Read before the Section on Radiology at the One Hundredth Annual Session of the American Medical Association, Atlantic City, June 13, 1951.

1. Spellberg, M. A., and Zivin, S.: Lymphosarcoma of the Gastrointestinal Tract, Arch. Int. Med. **83**:135 (Feb.) 1949. McSwain, B., and Beal, J. M.: Lymphosarcoma of the Gastro-Intestinal Tract, Ann. Surg. **119**:108, 1944. Yarnis, H., and Colp, R.: Lymphosarcoma of the Stomach, Gastroenterology **1**:1022, 1943.

2. (*a*) Minnes, J. F., and Geschickter, C. F.: Benign Tumors of the Stomach, Am. J. Cancer **28**:136, 1936. (*b*) Rigler, L. G., and Ericksen, L. G.: Benign Tumors of the Stomach, Radiology **26**:6, 1936. (*c*) Eusterman, G. B., and Senty, E. G.: Benign Tumors of the Stomach, Surg., Gynec. & Obst. **34**:5, 1922. (*d*) Rieniets, J. H.: Frequency and Pathologic Aspects of Gastric Leiomyoma, Proc. Staff Meet., Mayo Clin. **5**:364, 1930.

3. Sahler, O. D., and Hampton, A. O.: Bleeding Associated with Extramucosal Tumors of the Stomach, Am. J. Roentgenol. **49**:442, 1943.

of the Presbyterian Hospital, New York. All five of our patients presented either symptoms or signs of gastrointestinal bleeding. In two patients (Cases 2 and 3), the bleeding was completely overlooked and the clinical problem presented itself as one of unexplained anemia.

Ulceration is common, probably as a result of necrosis due to inadequate circulation when the tumor reaches a certain critical size. According to Stout's series, 30% of the patients have ulcers or ulcer symptoms. Two of our five patients had large ulcer craters (Cases 3 and 5), but only one (Case 1) complained of ulcer-like symptoms. The latter also had a hiatus hernia, which may have been responsible for his dyspepsia.

Only one patient (Case 3) had a palpable abdominal mass, although two others (Cases 4 and 5) had large masses demonstrable on roentgenologic examination.

The histological differentiation between benign and malignant neoplasm may be difficult in any given case. According to Golden and Stout,[4] if there are more than two miotic figures present per field, the tumor is probably malignant. If two or less are present, the malignant tendency, although less likely, is still not excluded. One

TABLE 1.—*Intramural Tumors of the Stomach*

Case No.	Sex	Age	Presenting Complaint	Duration	Clinical Findings	Pathological Diagnosis
1	M	54	Ulcer-like distress Massive hematemesis	3 mo. 1 day	Anemia Mild shock	Encapsulated leiomyoma
2	F	13	Anemia	6 mo.	Hypochromic anemia; occult blood in stool	Hemorrhagic leiomyoma
3	F	65	Anemia	2 yr.	Epigastric mass; hypochromic anemia	Large, ulcerated leiomyoma
4	M	38	Repeated gastrointestinal hemorrhages	1 yr.	Occult blood in stool	Hemorrhagic leiomyoma
5	F	54	Asthenia and melena	7 mo.	Mild anemia; normal gastric acidity	Ulcerated leiomyoma; ? leiomyosarcoma*
6	F	70	Anemia and melena	4 yr.	Anemia; occult blood in stools	Subserosal lipoma

* Weight loss, back pain, and hepatomegaly when seen eight months postoperatively.

of our patients (Case 5), whose tumor was considered benign histologically, has presented a subsequent clinical course indicative of malignant growth.

B. *Roentgenologic Features.*—The roentgen criteria for diagnosis of intramural tumors of the stomach have been concisely stated by many authors [6] and may be illustrated by one of our cases (Fig. 1). The characteristic findings are (1) demonstration of a sharply circumscribed, smooth, intraluminal filling defect, with or without an associated soft-tissue mass projecting beyond the contours of the stomach; (2) abrupt obliteration of gastric rugae over the tumor, with preservation of normal architecture in the immediate surrounding area; (3) preservation of pliable gastric walls and peristaltic activity, and finally, (4) ulceration in the central portion of the tumor in some of the cases.

Rigler [2b] stressed the value of administration of small amounts of barium sulfate suspension, compression, and overpenetration of the roentgenogram in roentgeno-

4. Golden, R., and Stout, A. P.: Smooth Muscle Tumors of the Gastro-Intestinal Tract and Retroperitoneal Tissues, Surg., Gynec. & Obst. **73**:784, 1941.

5. Footnote deleted.

6. Rigler and Ericksen.[2b] Sahler and Hampton.[3] Moore, A. B.: A Roentgenological Study of Benign Tumors of the Stomach, Am. J. Roentgenol. **11**:61, 1924.

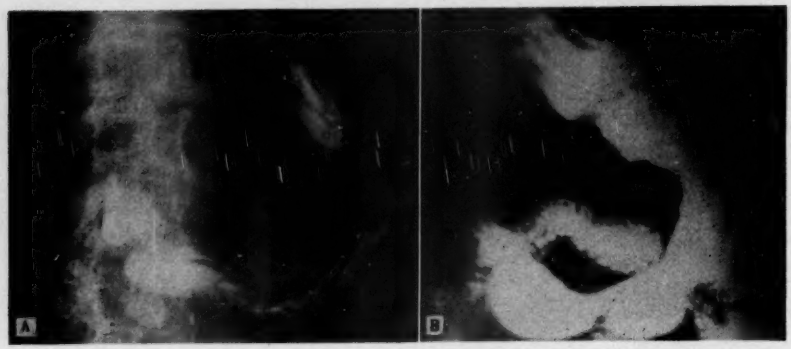

Fig. 1.—Gastric leiomyoma in a 65-year-old woman complaining of anemia of two years' duration. *A*, "mucosal relief" of stomach. *B*, right anterior oblique view of the barium-filled stomach.

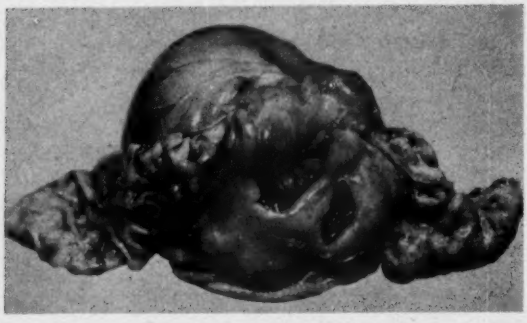

Fig. 2.—Surgical specimen from patient illustrated in Figure 1. The large gastric mass with a double crater on its mucosal surface is easily seen. Histological diagnosis was leiomyoma.

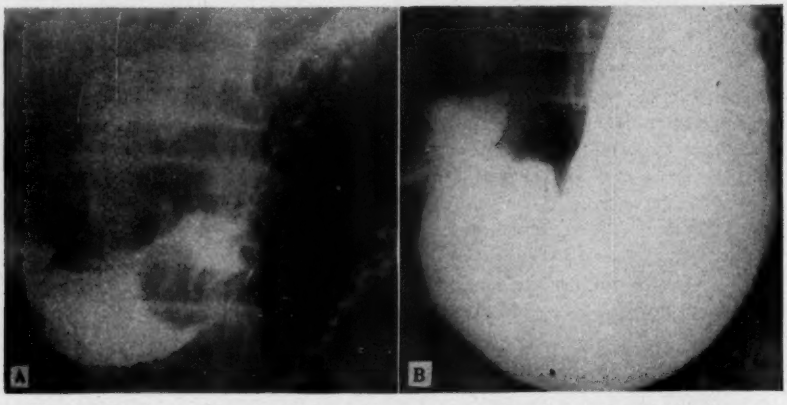

Fig. 3.—Roentgenograms of a 54-year-old man two weeks prior to an episode of gastrointestinal hemorrhage. Surgical pathological diagnosis was leiomyoma of the stomach. *A*, stomach partially emptied of the barium sulfate meal. *B*, barium-sulfate-filled stomach.

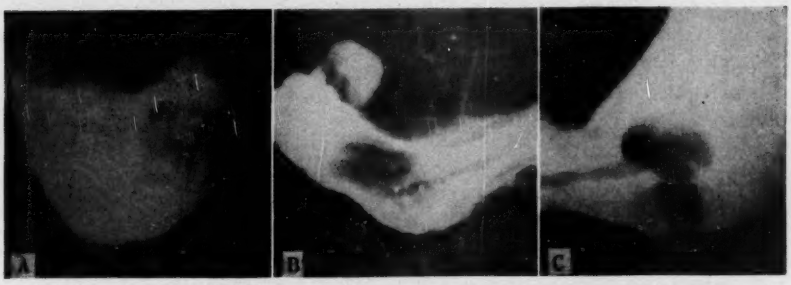

Fig. 4.—*A*, leiomyoma of the stomach. *B*, subserosal lipoma of the stomach. *C*, benign gastric adenoma.

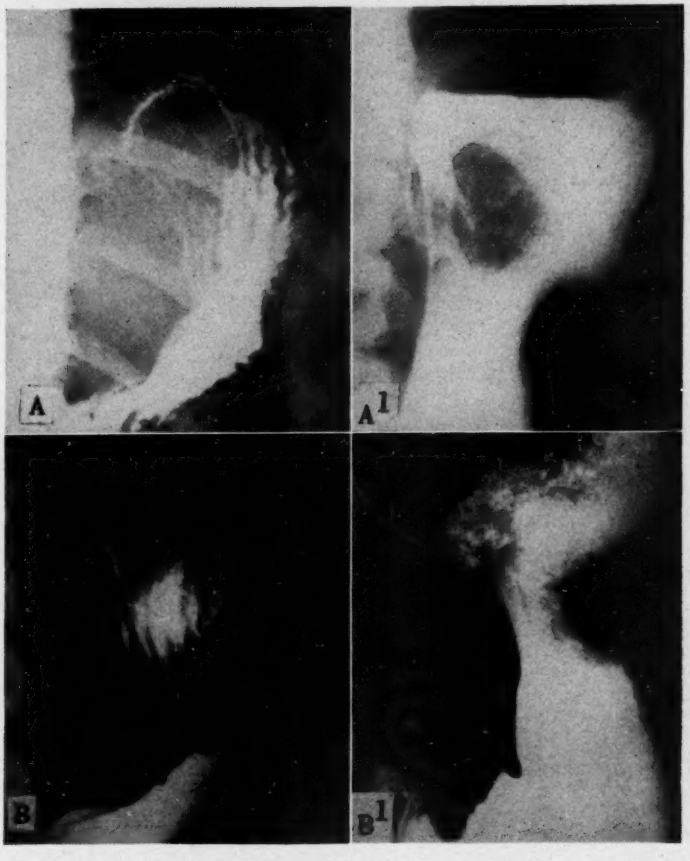

Fig. 5.—*A*, proved leiomyoma of the stomach in a 13-year-old girl with anemia. *B*, carcinoma of the stomach metastatic to liver and regional nodes in a 36-year-old woman.

logic diagnosis. Figure 3 emphasizes the validity of this observation. Both roentgenograms were made at the same examination, but the lesion is apparent only when the stomach is partially empty.

Differentiation of leiomyomas from other intramural lesions and wide-based adenomatous polyps is sometimes difficult. Figure 4 illustrates a leiomyoma, a subserosal lipoma, and a benign gastric adenoma. The adenoma, in this instance, was lobulated, and its intraluminal movement could be demonstrated under fluoroscopic manipulation. The lipoma was indistinguishable from a leiomyoma, even though slight movement within the gastric wall, said to be characteristic of lipomas, was demonstrable.

Epithelial tumors can, on occasion, fulfill all the roentgen criteria for intramural tumors. Lowman and Shapiro [7] described three such cases of gastric carcinoma. Figure 5 illustrates this similarity. No differentiating features are apparent, and both cases were diagnosed as leiomyoma of the stomach roentgenologically.

Occasionally, extragastric masses producing extrinsic pressure defects on the gastric wall, as well as intragastric foreign bodies, may also strongly suggest an intramural tumor.

TABLE 2.—*Primary Lymphosarcoma of Stomach: Data on Ten Cases*

Sex	Age Range, Yr.	Presenting Complaints	Duration	Clinical Findings	Preroentgen Diagnosis	Roentgen Diagnosis	Pathological Diagnosis
M 7 F 3	45-75 (average, 59)	Pain.....10 Weight loss.. 6 Bleeding..... 5	2 wk. to 5 yr. (average, 11.7 mo.)	Anemia..... 6 Mass..... 5 Occult blood in stools.... 3 Achlorhydria 4 of 6 patients tested	Carcinoma of stomach.... 4 Carcinoma of colon..... 2 Peptic ulcer.. 2 Pancreatitis. 1 Blood dyscrasia... 1	Carcinoma of stomach....10 Sarcoma suspected... 2	Large or multiple ulcers 6 of 8 Lymphosarcoma..... 8 Reticulum-cell sarcoma.... 2

Diagnoses on gastroscopy in two cases were carcinoma in one and gastric ulcer, with mention of lymphoma, in one.

LYMPHOSARCOMA

In contrast to the relatively well-defined clinical and roentgenologic picture presented by the leiomyomas, the manifestations of lymphosarcoma are definitely protean. This group of neoplasms must first be divided into two somewhat indistinct groups, i. e., those of primary origin in the stomach and those which secondarily involve this organ as part of a more generalized disease. Sugarbaker and Craver,[8] in reviewing 196 cases of unclassified lymphosarcoma, found 3% of primary origin in the stomach and 2% which had involved the stomach secondarily.

A. *Primary Lymphosarcoma of Stomach.*—The age range, symptomatology, and clinical findings presented by our group of 10 primary lymphosarcomas of the stomach (Table 2) are practically identical with those of any similar group of carcinomas. It is interesting to note that pain and bleeding are frequent complaints in spite of the supposed submucosal nature of the tumors. Large or multiple ulcerations found in six of the eight cases, which were completely studied as surgical pathological specimens, are the probable explanation for these findings.

7. Lowman, R. M.; Shapiro, R., and Kushlan, S. D.: Extramucosal Tumors Simulated by Gastric Carcinoma, Am. J. Roentgenol. **57**:726, 1947.

8. Sugarbaker, E. D., and Craver, L. F.: Lymphosarcoma, J. A. M. A. **115**:17 (July 6) 1940.

Gastroscopy was of little aid in two cases in which it was performed, although in one of the cases the possibility of lymphoma was suggested because of the presence of multiple ulcerations.

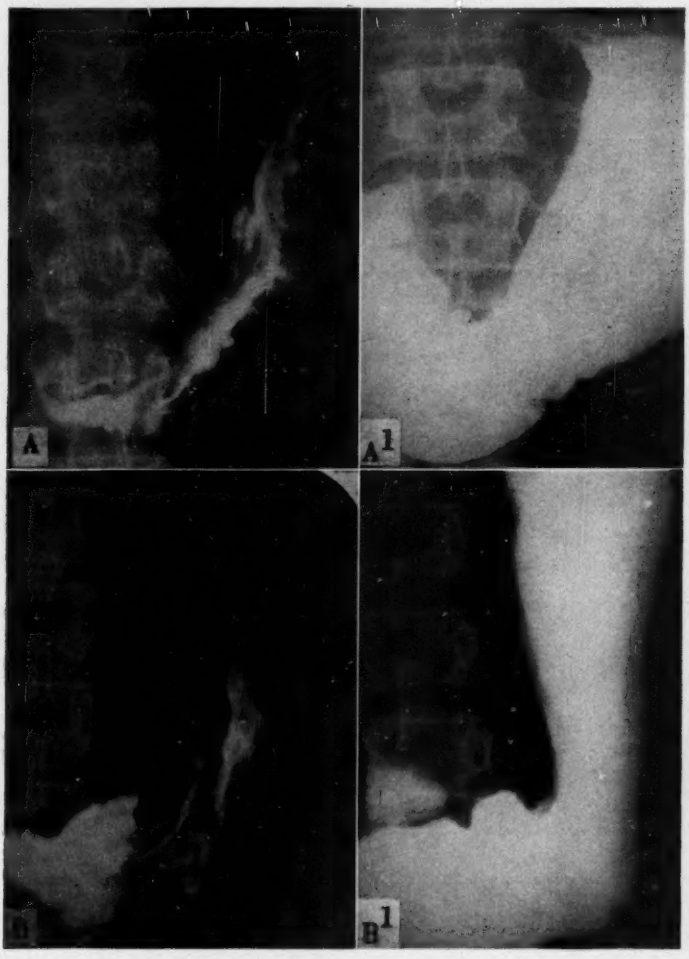

Fig. 6.—*A*, primary lymphosarcoma of the stomach in a 46-year-old man. *B*, proved infiltrative carcinoma of the stomach in a 49-year-old woman.

The clinical diagnoses ranged from carcinoma to pancreatitis, but in no instance included lymphoma as the initial impression.

B. *Roentgen Diagnosis.*—Exact roentgenologic diagnosis is also difficult. All our cases were diagnosed as carcinoma of the stomach by roentgenology, and in only two cases was lymphosarcoma suggested as a second possibility.

The marked variations in the gross pathological anatomy of this group of neoplasms account for the major source of diagnostic errors. Taylor,[9] in reviewing 152 primary lymphosarcomas of the stomach collected from the literature, classified them into those having (*a*) solitary or multiple ulcers with surrounding infiltration, (*b*) solitary or multiple nodular tumors in the submucosa, and, finally, (*c*) diffuse thickening of the entire stomach. The last constituted only 10% of the cases in his series. Unfortunately, it is only this small group of tumors which produces the so-called characteristic roentgen findings of lymphosarcoma.

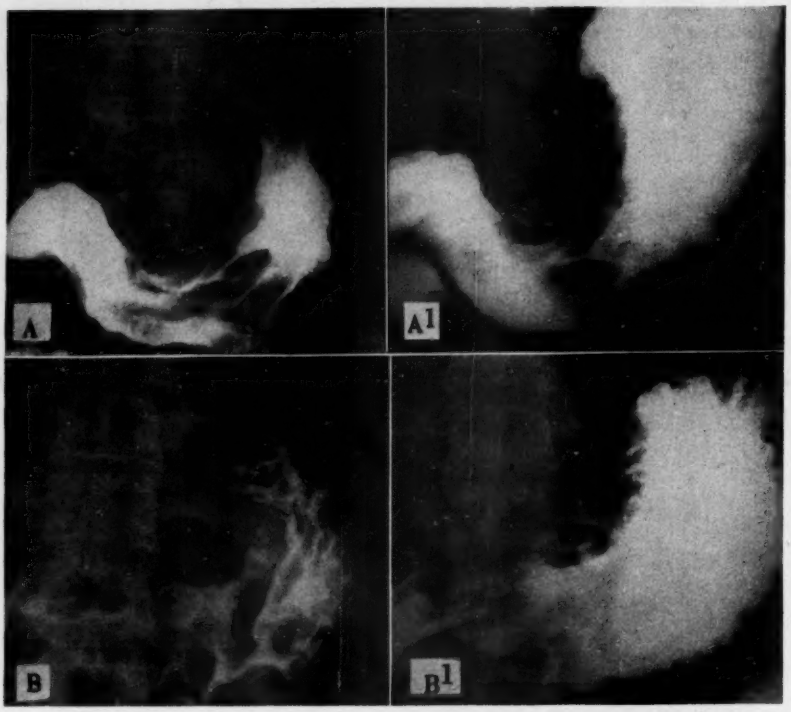

Fig. 7.—*A*, diffuse type of primary lymphosarcoma of the stomach in a 75-year-old woman. *B*, gastric ulcer and marked hypertrophic gastritis in a 38-year-old man.

The difficulty in differential diagnosis in the majority of cases is illustrated by comparing the roentgenographic picture of a case of lymphosarcoma with that of a case of carcinoma (Fig. 6). In both examples, there are obliteration of the mucosal pattern and straightening and stiffening of the gastric wall along the lesser curvature —the classic picture of infiltrative carcinoma. Fortunately, in most such instances, a roentgenologic diagnosis of malignant tumor can be made. This should lead to surgical exploration, and the correct histological diagnosis can then be made by the pathologist, even if surgical resection is not feasible.

9. Taylor, E. S.: Primary Lymphosarcoma of the Stomach, Ann. Surg. **110**:200, 1939.

The differentiation of the less common, diffuse type of lymphosarcoma from diffuse hypertrophic gastritis may also be impossible from roentgenographic or gastroscopic findings. Figure *7A* represents an example of the so-called classic picture of lymphosarcoma. These roentgenograms are from one of two cases in which we were able to suggest that possibility correctly. The broadened, exaggerated rugal folds, extensive involvement, somewhat pliable walls, and a filling defect are well demonstrated. However, there is very little roentgenographic distinction between this case and the case represented by Figure *7B*. The second case is one of gastric ulcer and marked hypertrophic gastritis. Diagnostic errors may be made in either direction.

C. *Secondary Lymphosarcoma of Stomach.*—Table 3 summarizes data on our seven cases of generalized lymphosarcoma with secondary involvement of the stomach. Three of the seven cases so classified may have been of primary origin in the stomach, since the gastrointestinal complaints preceded the clinical evidence of generalized involvement in each instance.

The age range and presenting gastrointestinal complaints are similar in the primary and secondary groups. Pain, weight loss, mass, and bleeding are common

TABLE 3.—*Secondary Involvement of Stomach by Lymphosarcoma: Data on Seven Cases*

Sex	Age Range, Yr.	Site of Primary Origin	Total Duration of Disease	Gastrointestinal Complaints	Duration of Gastrointestinal Symptoms	Roentgen Diagnosis
M 3 F 4	31-72 (average, 57)	Generalized..... 3 Tonsil..... 2 Rectum..... 1 Small intestine..... 1	1-5 yr.	Pain..... 5 Weight loss..... 4 Mass..... 3 Bleeding..... 2 Perforation..... 1	1 day to 5 yr.	Lymphosarcoma.... 1 Lymphosarcoma with ulceration..... 3 Involvement of other parts of gastrointestinal tract..... 3

to both. One of the seven cases in this group presented symptoms of acute perforation of a sarcomatous ulcer.

The secondary lymphosarcomas present less difficulty in roentgenologic differentiation, and, by proper correlation of all clinical and roentgen findings, we were able to establish the correct diagnosis in all seven cases.

Five of the seven patients were either suspected of having or known to have had lymphomatous or leukemic involvement of other organs prior to the gastrointestinal examination. When an ulcerative or infiltrative lesion of the stomach is demonstrated in such circumstances, the differential diagnostic probabilities are simplified and the diagnosis of lymphomatous involvement of the stomach is justifiable (Fig. 8). It is interesting to note that the largest ulcer craters demonstrable by roentgenologic techniques were found in the secondary group.

In the remaining two cases of this group, the extent of involvement of the gastrointestinal tract was of sufficient diagnostic significance to lead to a correct diagnosis of lymphosarcoma. Figure 9 illustrates not only gross infiltration of the entire stomach and a large ulcer crater on the greater curvature, but infiltration of the duodenum and jejunum as well in a patient with generalized lymphosarcoma. Such extensive involvement is totally out of character for carcinoma of the stomach.

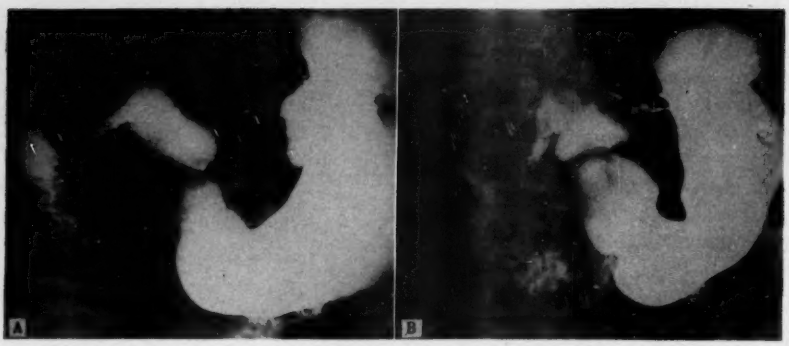

Fig. 8.—*A*, initial roentgenogram of a 67-year-old woman known to have had both lymphosarcoma of the tonsil and generalized lymphatic leukemia. *B*, same case two months after a course of external roentgen therapy directed to the stomach, illustrating complete healing of the ulcer.

Fig. 9.—Roentgenogram of a 31-year-old man in the terminal phase of generalized lymphosarcoma.

SUMMARY

An unusual experience with mesenchymal tumors of the stomach is reviewed. This experience indicates the following:

1. Benign intramural tumors of the stomach are important causes of gastrointestinal bleeding.

2. The roentgen criteria for the recognition of such tumors, although fairly accurate, are not pathognomonic.

3. The clinical and roentgenologic recognition of primary malignant mesenchymal tumors of the stomach is difficult in the majority of instances.

4. Histological examination offers the only accurate method for differentiation of these neoplasms from malignant epithelial tumors.

5. The extent of involvement or a previous diagnosis of generalized lymphomatous disease usually leads to the correct diagnosis in those patients with secondary sarcomatous involvement of the stomach.

TREATMENT OF THYROTOXICOSIS WITH 1-METHYL-2-MERCAPTOIMIDAZOLE

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THIS report deals with the use of 1-methyl-2-mercaptoimidazole in the treatment of thyrotoxicosis. Figure 1 shows its structural formula, and, with it, that of 6-*n*-propylthiouracil. There were 32 selected thyrotoxic patients in our series. Fifteen had been previously treated with iodine or a thiouracil; all except two, however, had completely relapsed on cessation of previous therapy. In both exceptions partial remission had been induced with methylthiouracil treatment. None represented examples of recurrent postoperative thyrotoxicosis.

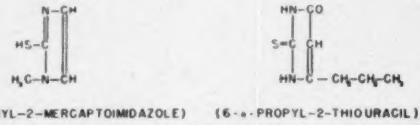

Fig. 1.—Structural formula of 1-methyl-2-mercaptoimidazole, as compared with that of 6-*n*-propyl-2-thiouracil.

CLINICAL MATERIAL

Our patients fall into two groups. In 17 treatment was begun with the hope of inducing a prolonged or permanent remission without operation. In 15 treatment was preoperative. Data on these groups are shown in the Table. In the first group the patients' ages ranged from 5 to 54 years. Three were children, aged 5, 5, and 8 years. Fourteen were females, and three males. Sixteen had diffuse goiters and one no palpable goiter. Five goiters were slight, and 11, moderate. Only one patient in this group was severely toxic. Five were mildly toxic, and 11, moderately toxic. In the preoperative group the patients' ages ranged from 17 to 63 years. All were women. Thirteen had diffuse goiters, and two had nodular goiters. Five glands were slightly enlarged; six, moderately enlarged, and 4, markedly enlarged. Five patients were severely toxic, and 10, moderately toxic. Both patients with nodular goiters were severely toxic with markedly enlarged glands.

Four patients receiving prolonged therapy began treatment in the hospital and then continued as outpatients, while five of the preoperative group were treated

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entirely as inpatients. All outpatients were seen in the beginning at two-week intervals. As their thyrotoxicosis subsided, they were seen once a month. Most patients had a basal metabolic rate determination and a leucocyte count at each visit. Hemoglobin determinations and differential leucocyte counts were done from time to time on many patients. No attempt was made to follow the serum cholesterol level.

Treatment in all adult patients of both groups was started with 30 mg. of methylmercaptoimidazole daily. Children initially received 15 mg. a day. The daily dose was divided into three equal parts given at eight-hour intervals. As thyrotoxicosis subsided, the dose was gradually reduced. In three patients given prolonged treatment the condition is maintained in remission by use of 5 mg. daily; they have been treated four to eight months and the period of remission has been three to six months. Of the remaining 12 patients on prolonged therapy now with remission, 11 are maintained on 10 to 20 mg. daily, while 1 receives 30 mg. a day; they have been treated 3 to 11 months, and their remissions range from less than 1 month to 8 months. Of two patients on prolonged therapy, without remission, one, a child, receives 15 mg. daily, while the other receives 45 mg. a day. This patient is the only one to receive as much as 45 mg. daily.

Classification of Thirty-Two Cases with 1-Methyl-2-Mercaptoimidazole Therapy

	No. of Cases	Types of Goiter		Degree of Thyroid Enlargement				Degree of Toxicity		
		Diffuse	Nodular	0	+	++	+++	+	++	+++
Prolonged use.....	17	16	0	1	5	11	0	5	11	1
Preoperative use.....	15	13	2	0	5	6	4	0	10	5

Ten preoperative patients ceased to take methylmercaptoimidazole on admission to the hospital. Five were previously taking 30 mg. a day, and five, 15 mg. daily. Five patients prepared for operation in the hospital continued methylmercaptoimidazole treatment until the day of operation. All preoperative patients except two received iodine for 7 to 10 days immediately before operation. One of these exceptions was the first patient prepared preoperatively. She did not receive iodine, because we wished to see what effect methylmercaptoimidazole alone would have on her thyroid. At operation her thyroid was found to be quite vascular and friable. In the other patient iodine was omitted because of known sensitivity.

RESULTS

The response of our patients was classified as good, fair, or poor. By a good response is meant a steady, progressive amelioration of the thyrotoxicosis with complete remission. A fair response is defined as one of considerable improvement, often not steadily progressive, without full remission. By a poor response is meant failure to show or maintain satisfactory improvement despite presumably adequate dosage.

Twenty-six patients showed a good response. Fifteen of these are on prolonged therapy and now experience complete remission. The minimum time required to induce complete remission was 4 weeks and the maximum time, 12 weeks, the average being 7 weeks. They have been treated 3 to 11 months. The period of remission for two has been seven to eight months; for five, four to six months; for seven,

two to three months; and for one, less than one month. No patient experienced remission long enough to stop the medication. Minimal evidence of partial relapse occurred in eight patients in the entire series when the dose was decreased. Their conditions were readily controlled again by increasing the dose. One, a child, received 7.5 mg., and the others were taking 10 to 20 mg. Six were receiving prolonged therapy.

Eleven patients treated preoperatively entered full remission. The minimum time required to induce remission in these patients was 4 weeks, and the maximum time, 16 weeks, the average being 9 weeks. Figure 2 shows a good preoperative response. This patient had a large nodular goiter and was severely toxic. After 16 weeks of methylmercaptoimidazole therapy, her thyrotoxicosis was considered clinically in remission despite slight tachycardia. Administration of iodine was started, and a few days later she was admitted to the hospital. Methylmercaptoimidazole treatment was then stopped. Her pulse rate soon became normal, and she was successfully operated on.

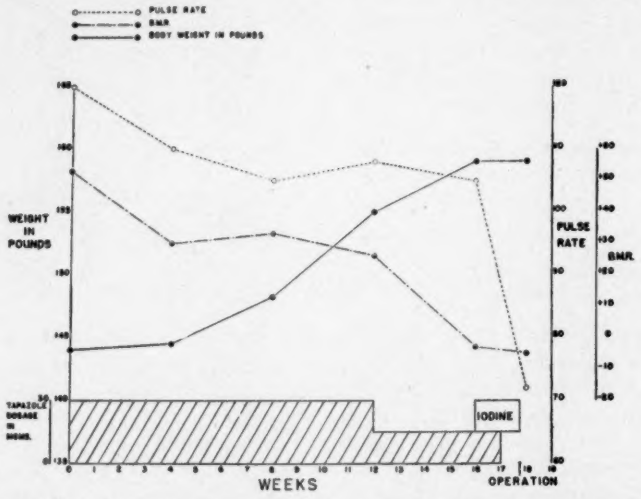

Fig. 2.—Clinical course of a thyrotoxic patient, a woman 42 years of age, prepared for operation with 1-methyl-2-mercaptoimidazole (methimazole ["tapazole"]) treatment.

Five patients showed only a fair response. Four of the five were hospitalized for rapid preoperative preparation. The condition of three had improved sufficiently in three weeks for them to undergo thyroidectomy; one required four weeks of treatment. None of these four yet had complete remission, but we believe this could have been attained with a longer period of preoperative treatment. Three had received iodine immediately prior to the start of methylmercaptoimidazole administration, so that this factor cannot be excluded as possibly retarding their response. The fifth patient was a 5-year-old girl under prolonged therapy. Despite seven months of treatment remission had not occurred, though she was much improved. Initially, she received 15 mg. of methylmercaptoimidazole daily for one week, and then the dose was arbitrarily halved. She continued six months

on this dose, improving but remaining slightly toxic. Her dose was then increased to 15 mg. daily, and when last seen she appeared to have almost complete remission of thyrotoxicosis. Her initial daily dose of 7.5 mg. was probably inadequate.

One patient has shown a poor response. She was 22 years old and severely toxic, with a firm, diffuse, moderately enlarged goiter. Remission had previously been induced with iodothiouracil treatment, but two attempts at operation had to be abandoned because of marked tachycardia under anesthesia. Later she relapsed and failed to respond to therapy with methylthiouracil. Administration of methylmercaptoimidazole was then started, and her subsequent progress is shown in Figure 3. She has now been receiving methylmercaptoimidazole for eight and one-half months. After six months of methylmercaptoimidazole therapy, almost complete remission occurred again followed by relapse and she is now receiving 45 mg. daily. When last seen, her condition was somewhat improved,

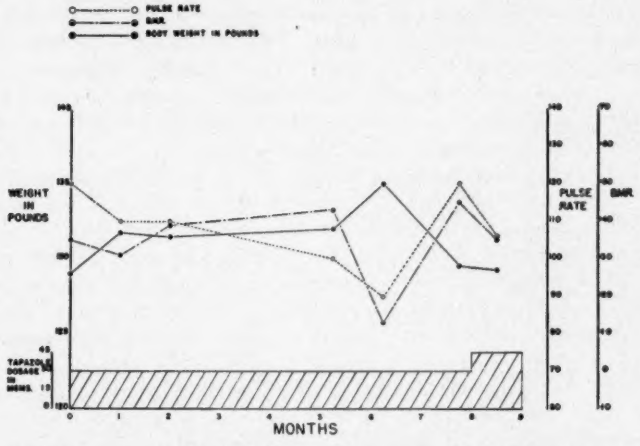

Fig. 3.—Clinical course of a thyrotoxic patient, a woman 21 years old, showing a poor response to treatment with 1-methyl-2-mercaptoimidazole (methimazole ["tapazole"]).

though far from a complete remission. There has been some uncertainty about her cooperation in taking the drug.

After treatment 9 goiters grew larger, while 10 became smaller. One goiter developed nodules. No change in size was noted in the remaining 12. Seven goiters became softer, while five grew firmer.

SENSITIVITY REACTIONS

Sensitivity reactions to methylmercaptoimidazole were minimal. One patient had generalized urticaria for a few days, but it cleared despite continued therapy, so that it might have been due to some unrecognized allergy. This patient later exhibited a weeping, vesicular skin eruption between two fingers of one hand, but when last seen this lesion was healing without interruption of therapy. Two patients had pruritus and a generalized maculopapular and vesicular eruption during treatment. One had pruritus before methylmercaptoimidazole therapy was

started and subsequently displayed an eruption while taking the drug. Conceivably, some other medicament, such as the barbiturates she received, could have produced this reaction. The other patient had pruritus and an eruption from iodine. Before the eruption had subsided, methylmercaptoimidazole therapy was begun. Soon thereafter the eruption became worse but gradually disappeared despite continued therapy.

No instances of leucopenia, granulocytopenia, drug fever, or other untoward reactions occurred.

COMMENT

The original work on the antithyroid potency of imidazoles in rats was reported in 1945 by Astwood, Bissell, and Hughes.[1] They found that 2-mercaptoimidazole was 1.5 times as potent as thiouracil. Evaluation of the potency of antithyroid compounds in experimental animals, however, has often given results quite different from those obtained clinically. In 1947 Stanley and Astwood [2] reported the relative antithyroid potencies of 32 compounds based upon their capacity to inhibit radioactive iodine uptake in normal man. They found 2-mercaptoimidazole the most potent of these compounds—ten times more potent than thiouracil. In 1949 these investigators,[3] using the same assay method, reported 1-methyl-2-mercaptoimidazole to be 100 times as potent as thiouracil. They also stated that it was highly effective in the treatment of 30 thyrotoxic patients.

T. H. McGavack and associates at the June, 1950, meeting of the American Medical Association showed in a Scientific Exhibit their results in the treatment of 60 thyrotoxic patients with methylmercaptoimidazole. They reported no toxic effects and good control of thyrotoxicosis, although 43% of the patients relapsed after cessation of therapy. They considered methylmercaptoimidazole the most satisfactory of antithyroid drugs and stated that it was approximately 35 times as potent as thiouracil. Initially they gave 15 mg. a day and then a maintenance dose of 2 to 10 mg. daily.

Reveno and Rosenbaum [4] in 1950 reported on the treatment of 18 thyrotoxic patients with methylmercaptoimidazole. They found it quite effective. The initial and maintenance doses for six previously untreated patients were 5 to 15 mg. daily. The time required for inducing remission was five to eight weeks.

Beierwaltes [5] also reported in 1950 the results of treatment with 1-methyl- and 1-ethyl-mercaptoimidazole in 20 thyrotoxic patients. The rate of fall in the basal metabolic rate averaged about 1% per day, compared with an average fall of 1% every 2.5 days with thiouracil and propylthiouracil therapy. He estimated that

1. Astwood, E. B.; Bissell, A., and Hughes, A. M.: Further Studies on the Chemical Nature of Compounds Which Inhibit the Function of the Thyroid Gland, Endocrinology **37**:456-482 (Dec.) 1945.

2. Stanley, M. M., and Astwood, E. B.: Determination of Antithyroid Compounds in Man Using Radioactive Iodine, Endocrinology **41**:66-85 (July) 1947.

3. Stanley, M. M., and Astwood, E. B.: 1-Methyl-2-Mercaptoimidazole: An Antithyroid Compound Highly Active in Man, Endocrinology **44**:588-590 (June) 1949.

4. Reveno, W. S., and Rosenbaum, H.: Treatment of Hyperthyroidism with 1-Methyl-2-Mercaptoimidazole, J. A. M. A. **143**:1407-1408 (Aug. 19) 1950.

5. Beierwaltes, W. H.: 1-Methyl-2-Mercaptoimidazole and 1-Ethyl-2-Mercaptoimidazole: A Clinical Evaluation of 2 New Antithyroid Drugs, J. Lab. & Clin. Med. **36**:861-865 (Dec.) 1950.

these compounds were more than seven times as effective as propylthiouracil by weight. No manifestations of sensitivity were observed.

Our experience suggests that the maintenance dose for adults with early remission may be somewhat higher than that stated by others and may vary from 10 to 20 mg. daily. We have found that remission can usually be induced in seven to nine weeks and maintained without difficulty. In general, the time required for remission seems related more to the degree of toxicity and the type of goiter than to the size of the gland. We believe patients with nodular goiters will require larger doses and longer therapy than patients with diffuse goiters of comparable toxicity. Previous treatment, excepting possibly recently administered iodine, had no apparent effect on the patient's response to methylmercaptoimidazole therapy.

SUMMARY

The results of treatment with 1-methyl-2-mercaptoimidazole over periods up to 11 months in 32 selected thyrotoxic patients are reported. Seventeen received prolonged therapy; 15 were given preoperative treatment.

Twenty-six patients showed a good response; 5, a fair response, and 1, a poor response. The time required to induce remission ranged from 4 to 16 weeks. Untoward reactions were limited to three patients and consisted of maculopapular and vesicular skin eruptions, urticaria, and pruritus. Factors other than the methylmercaptoimidazole administered may have been responsible for these reactions.

ADDENDUM

Since the above was written, several additional reports on the clinical use of methimazole have appeared. Bartels and Sjogren [6] and Hallman and Bondy [7] have confirmed its effectiveness, although the former report the incidence of sensitivity reactions as 6% in 100 patients.

Astwood [8] has reported satisfactory response to methimazole therapy in three cases of thyrotoxicosis associated with pregnancy.

The supply of 1-methyl-2-mercaptoimidazole was provided by Eli Lilly & Company, Indianapolis 6.

6. Bartels, E. C., and Sjogren, R. W.: 1-Methyl-2-Mercaptoimidazole: New Active Antithyroid Agent, J. Clin. Endocrinol. **11**:1057-1062 (Oct.) 1951.

7. Hallman, B. L., and Bondy, P. K.: Experience with Methimazole (Tapazole) in the Treatment of Hyperthyroidism: A Report of 35 Cases, Am. J. Med. **11**:724-729 (Dec.) 1951.

8. Astwood, E. B.: Use of Antithyroid Drugs During Pregnancy, J. Clin. Endocrinol. **11**:1045-1056 (Oct.) 1951.

STUDIES ON STREPTOCOCCAL HYALURONIDASE AND ANTIHYALURONIDASE

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THERE have been numerous reports in recent years dealing with hyaluronic acid, hyaluronidases, and hyaluronidase inhibitors. The relationship of these substances to Group A hemolytic streptococcal infections and rheumatic fever has been the chief interest of this laboratory. The present study was undertaken in an effort to gain additional information regarding this aspect of the problem.

The mucin-clot-prevention method was used to measure both streptococcal hyaluronidase and streptococcal antihyaluronidase. This method has been described by McClean [1] and was based upon the observations of Meyer and Palmer,[2] Seastone,[3] and Robertson, Ropes, and Bauer.[4] The basis of the test was the observation that hyaluronic acid, when mixed with protein and acidified, produced a mucin clot and that this reaction was inhibited by the presence of hyaluronidase. This test has been employed by subsequent investigators [5] and modified by us as described below.

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This investigation was performed, in part, under contract with the Commission on Acute Respiratory Diseases, Armed Forces Epidemiological Board; aided by a grant from the Life Insurance Medical Research Fund, and supported in part by a research grant from the National Heart Institute of the National Institutes of Health, United States Public Health Service.

1. McClean, D.: Studies on Diffusing Factors: 2. Methods of Assay of Hyaluronidase and Their Correlation with Skin Diffusing Activity, Biochem. J. **37**:169, 1943.

2. Meyer, K., and Palmer, J. W.: On Glycoproteins: Polysaccharides of Vitreous Humor and of Umbilical Cord, J. Biol. Chem. **114**:689, 1936.

3. Seastone, C. V.: The Virulence of Group C Hemolytic Streptococci of Animal Origin, J. Exper. Med. **70**:361, 1939.

4. Robertson, W.; Ropes, M. W., and Bauer, W.: Mucinase: Bacterial Enzyme Which Hydrolyzes Synovial Fluid Mucin and Other Mucins, J. Biol. Chem. **133**:261, 1940.

5. (*a*) Friou, G. J., and Wenner, H. A.: On the Occurrence in Human Serum of an Inhibitory Substance to Hyaluronidase Produced by a Strain of Hemolytic Streptococcus, J. Infect. Dis. **80**:185, 1947. (*b*) Quinn, R. W.: Studies of the Mucin-Clot Prevention Test for the Determination of the Antihyaluronidase Titer of Human Serum, J. Clin. Invest. **27**:463, 1948. (*c*) Harris, T. N., and Harris, S.: Studies in the Relation of the Hemolytic Streptococcus to Rheumatic Fever, Am. J. M. Sc. **217**:174, 1949. (*d*) Lapin, L., and Starkey, H.: Hyaluronidase Inhibitor Substances in Sera from Patients with Rheumatic Disease, Canad. M. A. J. **60**:468, 1949. (*e*) Pike, R. M.: Personal communication to the authors, 1949.

METHODS

1. *Preparation of Hyaluronic Acid.*—Human umbilical cords[6] were used as the source of hyaluronic acid. A jar containing acetone was kept in the obstetrical delivery room. The nurses were instructed to wash the umbilical cords under tap water and place them in the jar of acetone directly after the delivery. Every one to two weeks the cords were collected, fresh acetone was substituted, and the cords were stored in air-tight vessels in the cold room at 4 C. They could be kept indefinitely in this state.

The hyaluronic acid was extracted in the following manner. The cords were removed from the cold room, and the acetone was decanted. They were then dried by pressure between two towels and cut with scissors into small segments of about 3 cm. each. At this point they were weighed. The weight was designated the initial weight and was important since subsequent calculations were based upon it.

The cords were quite tough since they had been stored in cold acetone. It was desirable to allow them to soak in distilled water at room temperature for about 1 hour to soften them. They were then passed through a large, power-driven meat grinder. The mince that was obtained was chopped with distilled water in a Waring blendor.® The total amount of distilled water added both for softening the cords and for passing them through the Waring blendor® was about 4 ml. per gram of cords (initial weight). The mince was then placed in a glass vessel, and chloroform was added to form a visible layer on the bottom. Extraction was allowed to proceed overnight at 4 C., and the mince was removed by filtration through gauze. An additional 1 to 2 ml. of distilled water per gram of cords (initial weight) was added to the mince that remained, and this was passed through the Waring blendor® and allowed to extract as before. This process was repeated until three to four extracts were obtained. These were mixed and saved, and the mince discarded. The pH of the combined extracts was about 8.3.

The extracts were allowed to dialyze against running tap water in cellophane® tubes for 36 hours. There was an increase in volume of about 5%. The dialysate was centrifuged at 3,000 rpm for 30 minutes, and the supernatant was pipetted off. This was the final product. It was gray, slightly tinged with red, and viscous, with a pH of about 6.4. The yield was 2.5 ml. per gram of cord (initial weight). It was distributed in glass tubes and stored in the frozen state at —20 C. Under such conditions, it was stable for at least six months.

The advantages of this method were its relative simplicity and the high yield of hyaluronic acid in a liquid form.

2. *Preparation of Streptococcal Hyaluronidase.*—The production of hyaluronidase by Group A hemolytic streptococci was quite variable. The strain used for the preparation of enzyme for antihyaluronidase determinations was known to form large amounts of this enzyme. It was obtained from Dr. Robert W. Quinn and was of Group A and Type 4. Stock cultures of this organism were preserved in the frozen state.

The formation of the enzyme was dependent upon the medium employed, the size of inoculum, the period of incubation, and possibly the amount of available oxygen. If the period of incubation was too long, or if a large inoculum was used with a shorter period of incubation, the pH of the medium fell so low that the enzyme was inactivated.[7] The most satisfactory media in our hands were Todd-Hewitt broth[7a] and our own routine laboratory liver-stomach digest broth containing 2.5% of whole sterile horse blood. These were superior to dextrose broth (difco®) and beef heart infusion broth (difco®). The addition of 10% Dubos' medium serum (difco®) resulted in decreased enzyme production.

Our stock supply of Group A, Type 4, streptococcal enzyme was prepared in the following manner: A single colony of the organism employed was subcultured to 10 ml. of blood broth and incubated aerobically at 37 C. for 24 hours. This served as the pilot tube, and its entire

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6. The umbilical cords were made available through the cooperation of the Department of Obstetrics and Gynecology, Stanford University School of Medicine.

7. Hale, C. W.: Studies on Diffusing Factors, Biochem. J. **38**:368, 1944.

7a. Todd-Hewitt broth is a meat infusion broth containing 0.2% dextrose, 2% proteose-peptone (difco®) and buffered by the addition, after autoclaving, of 0.2% sodium bicarbonate as a sterile solution.

contents were used to seed 1 liter of the same medium contained in a large vessel to provide a large surface and maximally aerobic conditions. This was incubated at 37 C. for 12 hours. The contents of the flask were transferred to sterile centrifuge tubes aseptically and centrifuged at 2,000 rpm for 30 minutes. The supernatant which contained the enzyme was decanted free of the organisms and passed through Seitz filters. The receiving vessel was immersed in an ice bath, since the enzyme has been shown to deteriorate at room temperature.[5d] Seitz filtration did not result in any measurable reduction in potency.

The filtrate represented the final product. It was amber in color, and its pH was 6.5. It was distributed in sterile, chemically clean glass tubes and preserved in the frozen state at —20 C. Storage in this manner for at least six months did not result in any loss of potency.

The hyaluronidase production of various strains of hemolytic streptococci was determined by picking a single colony to tubes containing 10 ml. of blood broth. After incubation for 12 to 24 hours the tube was centrifuged for 15 minutes at 2,000 rpm, and the supernatant was removed and preserved in the frozen state at —20 C. until tested in suitable dilutions by the method to be described.

3. *Measurement of Streptococcal Hyaluronidase.*—The reagents used in the test included:

1. Hyaluronic acid. This was prepared and preserved as described earlier. A fresh tube was allowed to thaw at 37 C. for each day's testing.

2. Dubos' medium albumin (difco®). This was kept in the cold room at 4 C.

3. Sorensen's phosphate buffer, M/15, pH 6.468.[8]

4. Isotonic sodium chloride solution, 0.9 gm. of sodium chloride per 100 ml. of distilled water.

5. Acetic acid, 4.35 N (1:4 dilution of glacial acetic acid).

Only triple-distilled water was used as the diluent in the preparation of the above reagents. Chemically clean glassware was used throughout.

The stock supply of Group A, Type 4, streptococcal hyaluronidase was standardized as follows. A fresh tube of enzyme was removed from the freezer and allowed to thaw at room temperature. The following dilutions were made in isotonic sodium chloride solution: 1:10, 1:100, 1:500, 1:1,000 1:2,000, and 1:4,000. Five-tenths milliliter of each of the above dilutions was used per tube. A control tube contained 0.5 ml. of isotonic sodium chloride solution without any enzyme. A substrate was prepared daily which contained the following proportions of the various reagents: 0.3 ml. of hyaluronic acid, 0.3 ml. of Dubos' medium albumin, and 0.9 ml. of Sorensen's buffer. A rack containing the tubes and a flask of substrate were placed in an ice bath for 5 minutes.

One and five-tenths milliliter of substrate was then added to each tube, including the control. Automatic pipettes were used whenever feasible. The rack of tubes was placed in a water bath at 35 to 37 C., allowed to incubate for 20 minutes, and cooled in an ice bath for 5 minutes. Two-tenths milliliter of 4.35 N acetic acid was added, and the tubes were shaken vigorously.

The test was read immediately in the following manner: The control tube was found to have a clearly visible good-sized mucin clot floating on the surface with a clear subnatant. Only turbidity was present when there was considerable enzyme activity. If there was partial digestion of the hyaluronic acid, shreds or small clots were present with a granular precipitate distributed throughout the tube, and, if there was no or minimal enzyme activity, the tube resembled the control. Those tubes which contained a large clot with a clear or faintly turbid subnatant were considered to be negative for enzyme activity. The tube with the highest dilution of enzyme which still showed enzyme activity was considered to be the end-point.

The original preparation of enzyme was active in a 1:500 initial dilution or 1:2,000 final dilution. The amount present in the last tube in which activity was present was arbitrarily defined as 1 unit of streptococcal hyaluronidase. Thus, 0.5 ml. of a 1:500 dilution of this lot contained 1 unit, and the titer was 1,000 units per milliliter.

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8. Thirty milliliters of a stock solution of anhydrous dibasic sodium phosphate containing 9.47 gm. per liter is added to 70 ml. of a stock solution of monobasic potassium phosphate containing 9.08 gm. per liter.

Testicular hyaluronidase[9] was used as a standard of comparison. The contents of a vial, 150 turbidity-reducing units in the dry state, were dissolved in 10 ml. of isotonic sodium chloride solution. The end-point with this preparation was the tube containing 0.5 ml. of a 1:200 dilution of the stock solution. Thus, 1 unit of streptococcal hyaluronidase was equivalent to 0.0375 turbidity-reducing unit, as measured by the mucin-clot-prevention technique.

4. *Determination of Streptococcal Antihyaluronidase.*—Serum was obtained in the usual way, using aseptic techniques, and was stored in the frozen state. At the time of testing the sera were allowed to thaw at room temperature. Two-tenths milliliter of serum was then added to 1.8 ml. of Sorensen's phosphate buffer, M/15, pH 6.428, to make an initial dilution of 1:10, and this was inactivated at 54 to 56 C. for 30 minutes. The following dilutions were prepared after heating, also in phosphate buffer: 1:50, 1:250, 1:1,250, and 1:6,250. These represented fivefold decrements of serum and were the smallest which could be used if satisfactorily clear-cut end-points were to be obtained.

In performing the test, 0.5 ml. of each serum dilution was added per tube. Five-tenths milliliter of a 1:200 dilution in saline of stock streptococcal hyaluronidase was then added to each of the tubes containing serum. Since the potency of this enzyme was 1,000 units per milliliter, this represented 2.5 units of streptococcal hyaluronidase per tube.

The two control tubes were set up as follows:

Control 1: 0.5 ml. of Sorensen's phosphate buffer
0.5 ml. of 1:200 dilution of enzyme

Control 2: 0.5 ml. of Sorensen's phosphate buffer
0.5 ml. of isotonic sodium chloride solution

The rack of tubes was shaken and allowed to remain at room temperature for 20 minutes. The tubes were then transferred to an ice bath and allowed to cool for 5 minutes. One milliliter of substrate which had been allowed to cool to this same temperature was added to each tube. This substrate had been prepared to contain the following amounts of reagents in 1.0 ml.:

0.3 ml. of hyaluronic acid
0.3 ml. of Dubos' medium albumin (difco®)
0.4 ml. of Sorensen's buffer, M/15

The tubes were placed in a 35 to 37 C. water bath and allowed to incubate for 20 minutes. They were then returned to the ice bath for 5 minutes. After removal from the ice bath, 0.2 ml. of 4.35 N acetic acid was added to each tube. The rack of tubes was shaken vigorously, and the test read immediately.

In reading the test it was noted that Control 1, which contained 2.5 units of enzyme, showed no clot, only shreds and granular precipitate. Control 2, which was void of enzyme, showed a large clot with a clear subnatant. Those tubes which contained a considerable amount of streptococcal antihyaluronidase resembled Control 2. Those tubes which contained little or no streptococcal antihyaluronidase resembled Control 1. The end-point was that tube which contained the highest dilution of serum that still exhibited a 3+ or 4+ clot and a clear, or slightly turbid, subnatant. This indicated that such a tube contained sufficient streptococcal antihyaluronidase to neutralize 2.5 units of enzyme. This amount of streptococcal antihyaluronidase was arbitrarily designated 1 unit.[10] A control serum was used, 0.5 ml. of which in an initial dilution of 1:50 neutralized 2.5 units of enzyme. Thus, the control serum had a titer of 100 units per milliliter.

By and large, the same titer was obtained on repeated testing with a given serum. Occasionally a one-tube variation was noted. The final concentration of salts in the tests was in the region of 0.09 M.

5. *Standardization of the Test.*—A new batch of hyaluronic acid was standardized by using varying amounts in the substrate and running simultaneous tests with the previous lot of hyaluronic acid against stock streptococcal hyaluronidase and testicular hyaluronidase.

9. The testicular hyaluronidase used in this study was provided by the Schering Corporation, Bloomfield, N. J., through the courtesy of Dr. Abbott W. Allen.

10. The unit value was twice the reciprocal of the effective initial dilution of serum.

In addition, six sera were tested simultaneously against the old substrate and against several substrates containing varying proportions of the new lot of hyaluronic acid. That substrate giving results identical with those obtained with the old substrate was selected to be used for future tests.

The streptococcal hyaluronidase was standardized by comparing it with the previous lot of enzyme. Various dilutions were then prepared which contained a final concentration of enzyme in the region of 5.0 units per milliliter. These preparations were then compared with the previous lot of enzyme by the simultaneous testing of 10 sera. The particular dilution which gave results identical with those obtained by a 1:200 dilution of the original enzyme was used in subsequent tests.

RESULTS

In Vitro Production of Hyaluronidase by Hemolytic Streptococci.—Crowley [11] found that only Types 4 and 22 of the Group A hemolytic streptococci produced hyaluronidase in vitro when measured by the mucin-clot-prevention technique. In view of this work it was difficult to account for the presence of neutralizing substances against streptococcal hyaluronidase in patients convalescing from clinical infections due to Group A hemolytic streptococci of other than Types 4 and 22.

Two explanations have been offered: 1. The methods of measurement were too crude to detect the production of small amounts of hyaluronidase. Recently, Pike [12] and Sallman and Birkeland [13] have shown that the formation of this enzyme is more widespread among Group A streptococci than was formerly believed. 2. The presence of hyaluronic acid in the host tissues enhanced the production of hyaluronidase by the infectious agent in vivo as it has been shown to do in vitro.[14]

A method was devised and has been described above that would measure small amounts of streptococcal hyaluronidase for the purpose of further exploring the first hypothesis. The organisms tested were hemolytic streptococci of Groups A, C, and G [15] isolated from the throats or skin of persons suffering from active clinical disease.

Initially an incubation period of 24 hours and dilutions of the supernatant from 1:1 (i. e., undiluted) through 1:500 were used. Fifty-two strains of Group A, nearly all untypable, were studied, of which 19 formed measurable hyaluronidase in a dilution of 1:1, and 3 in a dilution of 1:500. Five strains of Group C and eight of Group G produced large amounts of the enzyme, activity being present in every instance in the 1:500 dilution.

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11. Crowley, N.: Hyaluronidase Production by Hemolytic Streptococci of Human Origin, J. Path. & Bact. **56**:27, 1944.

12. Pike, R. M.: Streptococcal Hyaluronic Acid and Hyaluronidase, J. Infect. Dis. **83**:1, 1948.

13. Sallman, B., and Birkeland, J. M.: The Role of Hyaluronidase in Hemolytic Streptococcal Infection, Ann. New York Acad. Sc. **52**:1062, 1950.

14. Sallman and Birkeland.[13] McClean, D., and Hale, C. W.: Studies on Diffusing Factors, Biochem. J. **35**:159, 1941. McClean, D.: The Capsulation of Streptococci and Its Relation to Diffusion Factor (Hyaluronidase), J. Path. & Bact. **53**:13, 1941. Rogers, H. J.: The Influence of the Hydrolysates of Hyaluronate upon Hyaluronidase Production by Microorganisms, Biochem. J. **40**:583, 1946.

15. Grouping and typing were done by the precipitin method of Lancefield and Swift, using sera supplied by United States Public Health Service, Communicable Disease Center, Chamblee, Ga.

Organisms were subsequently incubated for only 12 hours and tested in serial dilutions from 1:1 through 1:16. Eighty-eight additional strains of Group A hemolytic streptococci were studied in this manner, and the results are shown in Table 1. The serologic type of 27 of these strains was determined by the precipitin method. Twenty-five, or 28.4%, of these strains produced demonstrable hyaluronidase, eight in large amounts. A few strains of Types 1, 12, 38, and 44 formed the enzyme. The others that were specifically classified were inactive.

In summary, 31% of 140 strains of Group A hemolytic streptococci from human sources produced demonstrable hyaluronidase, usually in small amounts.

Specificity of Streptococcal Antihyaluronidase.—Hyaluronidases were prepared from the following bacterial sources in a manner similar to that used for the preparation of streptococcal hyaluronidase for the purpose of studying their immunological specificity: (1) Pneumococcus, Type 5, (2) Staphylococcus (Micrococcus) pyogenes var. aureus, coagulase-positive, (3) hemolytic Streptococcus, Group B, and (4) hemolytic Streptococcus, Group G.

TABLE 1.—*Production of Hyaluronidase by Group A Streptococci in Vitro*

Serologic Type	No. of Strains	Dilution Titer						
		0	1:1	1:2	1:4	1:8	1:16	>1:16
1	3	2	1	..	..	..	..	..
6	2	2	..	..	..	..	..	..
12	8	5	1	..	2	..	..	..
38	1	..	..	..	..	..	..	1
41	1	1	..	..	..	..	..	..
44	12	10	2	..	..	..	..	..
Untypable	61	43	8	2	1	..	..	7
Total	88	63	12	2	3	..	..	8

The potency of these enzymes was determined as described for Group A, Type 4, streptococcal hyaluronidase, and a comparable amount of enzyme was used for the determination of antihyaluronidase. Four sera with high titers of antihyaluronidase against Group A, Type 4, Streptococcus were chosen and tested against the bacterial enzymes mentioned above, as well as against testicular hyaluronidase prior to and after heating at 54 to 56 C. for 30 minutes. The results are shown in Table 2.

Analysis of Table 2 revealed the following salient points:

1. Group A streptococcal antihyaluronidase was specific for Group A streptococcal hyaluronidase and did not neutralize enzymes prepared from the other sources. It was heat-stable.

2. Group G hyaluronidase was not inhibited by Group A antihyaluronidase.

3. Testicular antihyaluronidase did not neutralize enzyme prepared from the Staphylococcus or from hemolytic streptococci of Broup B and G. It was heat-labile.

4. All the sera exhibited pneumococcal antihyaluronidase activity, but the titers bore no direct relationship with the Group A streptococcal antihyaluronidase titers. This ability to neutralize pneumococcal hyaluronidase was not diminished by heating.

The above findings were in essential agreement with those reported by McClean [1] and Friou.[16] Further study by the latter author suggested that Group A streptococcal antihyaluronidase was group-specific, but not type-specific.

Unless stated otherwise, further remarks regarding streptococcal antihyaluronidase will refer to Group A streptococcal antihyaluronidase.

Streptococcal Antihyaluronidase in Health.—1. Newborn Infants: Sera were available in the frozen state which had been obtained from pregnant women at term and from the cord bloods of their newborn infants. Twenty-five sera from mothers whose antistreptolysin O titers were 100 units per milliliter or greater were selected, and the streptococcal antihyaluronidase content of these and of the corresponding cord bloods was determined.

TABLE 2.—*Neutralization of Various Hyaluronidases by Human Serum*

	Human Serum No.							
	A-Z		P-67		R-5		R-6	
Source of Enzyme	Unheated	Heated at 56 C. for 30 Min.	Unheated	Heated at 56 C. for 30 Min.	Unheated	Heated at 56 C. for 30 Min.	Unheated	Heated at 56 C. for 30 Min.
Group A, Type 4, hemolytic Streptococcus	100	100	500	500	500	500	2,500	2,500
Group B hemolytic Streptococcus	100	100	< 20	< 20	< 20	< 20	< 20	< 20
Group G hemolytic Streptococcus	< 20	< 20	< 20	< 20	< 20	< 20	< 20	< 20
Staph. pyogenes var. aureus, coagulase-positive	< 20	< 20	< 20	< 20	< 20	< 20	< 20	< 20
Pneumococcus, Type V	20	20	20	20	100	100	20	20
Testicular hyaluronidase	< 20	< 20	20	< 20	20	< 20	< 20	< 20

TABLE 3.—*Streptococcal Antihyaluronidase Titers in Healthy Medical Students*

No. of Students	Titer (in Units per Ml. of Serum)
40	< 20
48	20
43	100
5	500
136	

In general, the antibody level of the newborn infant approximated that of the mother. There was a tendency for the cord bloods to have slightly higher titers of both antihyaluronidase and antistreptolysin O than their corresponding maternal sera.

2. Children 6 Months of Age: The sera of six infants who had measurable streptococcal antihyaluronidase at birth were selected. In four of these, the titers were 100 units per milliliter; the remaining two had titers of 20 units per milliliter. The sera of none of these infants had any measurable streptococcal antihyaluronidase when examined at 6 months of age.

3. Adults: The sera of 136 healthy medical students were tested, and the results are shown in Table 3. There was a fairly even spread in the range of less than 20 to 100 units per milliliter. A titer of 500 units per milliliter was unusual.

16. Friou, G. J.: Further Observations of an Inhibitor in Human Serums of the Hyaluronidase Produced by a Strain of Hemolytic Streptococcus, J. Infect. Dis. **84**:240, 1949.

This general pattern of streptococcal antihyaluronidase, reflecting the level of the mother at birth, disappearing in early infancy, and reappearing in adult life, has been noted by other observers [17] and is characteristic of antibodies.

Streptococcal Antihyaluronidase Following Group A Hemolytic Streptococcal Infection in Children.—The antistreptolysin O response following hemolytic Streptococcus infection in early childhood was described in a previous paper.[18] Roughly the same group of patients was used in the present study. Selection of patients for inclusion in the study was based entirely on availability of adequate clinical, bacteriological, and serologic material.

Adequate information was available on 57 children who had been followed through 63 infections due to Group A hemolytic streptococci. The clinical manifestations of infection were varied and included pharyngitis and tonsillitis, impetigo, otitis media, wounds, and vaginitis. All the children were under the age of 8 years. None had rheumatic fever or glomerulonephritis. Many received penicillin in the course of their illness, very often after the peak of antistreptolysin O response had been attained.

It was useful, for purposes of analysis, to compare the antihyaluronidase titers with the antistreptolysin O levels. Three patterns of antistreptolysin O response were described in the report referred to above.[18] Pattern I was characterized by a feeble response, the peak level never rising above 12 units per milliliter. Pattern II was characterized by a slight to moderate antibody response, with a mean peak titer of 235 units per milliliter, falling rapidly to low levels of 12 units in all but two cases in one to four months. Pattern III was distinguished by a vigorous antibody response. The mean peak titer was 495 units per milliliter, and titers of 100 units per milliliter or greater were maintained for more than four months.

Increasing vigor of the antibody response was correlated with age. A few children were observed who had several infections before the age of 3 years. With the initial infection they exhibited Pattern I. They displayed Patterns II and III in subsequent infections, suggesting that conditioning to the antibody-forming tissues by reinfection was responsible for the changing antibody responses.

The infections were classified on the basis of the antistreptolysin O response into the various patterns described above. The antihyaluronidase values obtained in each group, as well as additional pertinent data, are summarized in Table 4. The in vitro hyaluronidase production of 52 of the 63 strains of streptococci was determined.

Analysis of the findings revealed the following points:

1. None of the subjects who were poor producers of antistreptolysin O (Pattern I) developed any measurable antihyaluronidase.

2. A few (11.0%) of the subjects whose antistreptolysin O response was moderate with poorly maintained levels (Pattern II) produced some antihyaluronidase.

3. Measurable to very large amounts of antihyaluronidase were formed by 92% of the subjects whose antistreptolysin O response was vigorous and well sustained (Pattern III).

17. Harris and Harris.[5c] Friou.[16]

18. Rantz, L. A.; Maroney, M., and Di Caprio, J. M.: Antistreptolysin O Response Following Hemolytic Streptococcus Infection in Early Childhood, A. M. A. Arch. Int. Med. **87**:360 (March) 1951.

4. The percentage of strains of streptococci which produced hyaluronidase in vitro was similar in each group.

Information was not available to define adequately the course of the serum antihyaluronidase titers with time. Very high levels (2,500 and 500 units per milliliter) often (five of six cases) declined one tube (to 500 or 100 units per milliliter) within three months after the onset of infection. Further decrements occurred only occasionally during the period of observation, but falls from 100 to 20 units per milliliter had occurred by the sixth month in 4 of 13 patients on whom suitable data were available.

It should be borne in mind that the method was able to detect only fivefold changes in antibody concentration.

TABLE 4.—*Relationship of Antihyaluronidase and Antistreptolysin O Responses Following Group A Hemolytic Streptococcal Infection in Early Childhood*

	Antistreptolysin O		
	Pattern I	Pattern II	Pattern III
Total number of patients	11	24	22
Total number of infections	12	27	24
Average age of patients, mo.	20.0	41.4	64.4
Units/Ml. Peak of Streptococcal Antihyaluronidase Titer	No. of Infections	No. of Infections	No. of Infections
< 20	12	24	2
20	0	1	3
100	0	2	9
500	0	0	6
2,500	0	0	4
% having no measurable antihyaluronidase	100.0	89.0	8.3
% of strains producing hyaluronidase in vitro	20.0	21.0	28.0

Streptococcal Antihyaluronidase in Rheumatic Fever.—Previous investigators [5a-d] have described striking elevations of the antihyaluronidase titers in the serum of human beings suffering from rheumatic fever. This has been particularly impressive early in the disease and in the presence of carditis. Additional observations on such patients have been made during the present study.

The antihyaluronidase and antistreptolysin O titers in a group with acute rheumatic fever of less than three months' duration have been compared with similar antibody levels in a group with active rheumatic fever of longer duration. Another group of children of comparable age and range of antistreptolysin O titers is included. These were children who were suspected of having rheumatic fever but, after study, were believed to have some other disorder or no disease. All the data are presented in Table 5. These cases were segregated on the basis of clinical and laboratory data without reference to the antibody determinations. The difficulties inherent in the precision diagnosis of rheumatic fever are clearly recognized, and errors in diagnosis were probably made. Nearly all the patients with a definite diagnosis of rheumatic fever had during the study period, or had had, evidence of carditis. A considerable additional group of children was excluded from consideration since it was impossible to make a satisfactory clinical diagnosis.

The antistreptolysin O titers in early rheumatic fever were elevated in varying degree as was to be expected from previous work. The antihyaluronidase levels were 100 units or greater in 16 of 17 cases and 500 units or more in 14 cases. One child 4 years of age with unquestionable acute rheumatic fever with atrioventricular dissociation but without arthritis following a hemolytic streptococcal respiratory infection did not develop measurable antihyaluronidase. Subsequently she was followed for 20 months. Two episodes of streptococcal respiratory infection occurred in a convalescent home; following one of them a recrudescence of arthritic rheumatic fever was observed. Serial antibody determinations were made at frequent intervals throughout this period, and detectable antihyaluronidase was never discovered, although there were vigorous antistreptolysin O responses on two occasions.

TABLE 5.—*Maximum Antihyaluronidase and Antistreptolysin O Titers in Early and Late Acute Rheumatic Fever and in Nonrheumatic Children*

Acute Rheumatic Fever of Less Than 3 Mo. Duration			Acute Rheumatic Fever of More Than 3 Mo. Duration				Patients in Whom Rheumatic Fever Was Not Present		
Age, Yr.	Anti-hyaluronidase, Units/Ml.	Anti-streptolysin O, Units/Ml.	Age, Yr.	Duration of Activity, Mo.	Anti-hyaluronidase, Units/Ml.	Anti-streptolysin O, Units/Ml.	Age, Yr.	Anti-hyaluronidase, Units/Ml.	Anti-streptolysin O, Units/Ml.
14.0	2,500	250	12.0	4	2,500	166	11.0	500	500
30.0	2,500	833	10.0	4	500	166	12.0	500	166
3.5	2,500	833	16.0	5	500	833	2.5	500	250
16.0	500	166	8.0	9	500	333	10.0	500	333
9.5	500	250	15.0	3	500	625	11.0	500	333
7.5	500	1,250	16.0	12	100	166	7.0	100	166
11.0	500	166	9.5	15	100	250	10.0	100	250
10.5	500	166	11.0	8	100	250	12.0	100	166
5.0	500	250	10.0	12+	100	625	6.0	100	250
13.5	500	625	6.0	6	20	500	10.0	100	166
6.0	500	500	9.0	6	20	100	5.0	100	250
13.5	500	333	....	..	...	...	7.0	20	500
9.0	500	250	....	..	...	...	6.0	20	500
15.0	500	166	....	..	...	...	7.0	20	166
3.0	100	166	....	..	...	...	5.0	20	166
10.5	100	166	....	..	...	...	6.0	20	250
4.0	< 20	166	....	..	...	...	8.0	20	500
....	...	...	....	..	...	...	5.0	< 20	500

The antihyaluronidase titers were also high in 11 cases of active, but not early, rheumatic fever. The serum concentrations in two were 20 units per milliliter and were 100 units per milliliter or more in the others.

High serum antihyaluronidase levels were present in many children with elevated antistreptolysin O titers who did not have rheumatic fever. This group differed from those including children with early and late active rheumatic fever. A higher incidence of low antihyaluronidase titers (20 units or less) and a decreased incidence of very high titers (2,500 units) occurred, and the mean titer was lower.

Overlapping of the values obtained in these children and in those with late active rheumatic fever was more marked than in the children with early rheumatic fever. This suggested that the rapid decline of antihyaluronidase from high level described earlier in the patients with uncomplicated streptococcal infection might be occurring in rheumatic subjects. This proved to be true in the cases in which suitable data were available. One-tube declines were demonstrated in five of nine early cases followed for five months.

COMMENT

The study of hyaluronic acid, hyaluronidases, and hyaluronidase inhibitors has aroused considerable interest in the last decade. This activity has been the result of the increased awareness of the fact that hyaluronic acid is an important constituent of connective tissue and that pathological change in these tissues occurs regularly in certain disease states. Among these are acute rheumatic fever, rheumatoid arthritis, disseminated lupus erythematosus, periarteritis nodosa, dermatomyositis, and scleroderma.

Hyaluronidases may be extracted from certain living tissues and are produced by many micro-organisms. Inhibitors of these enzymes are present in the serum of human beings and are of two types. The first are heat-labile and nonspecific and are not antibodies. The second neutralize specifically the hyaluronidases of various micro-organisms, are heat-stable, and probably are true antibodies.

This report is concerned with streptococcal hyaluronidase, an enzyme produced by certain hemolytic streptococci which depolymerizes hyaluronic acid, and its specific antihyaluronidase.

Study of the mucin-clot-prevention method for the measurement of hyaluronidases and their inhibitors led to a simplification of the technique for the preparation of the hyaluronic acid substrate from human umbilical cords. Salt concentration and pH of the reactive system were found to be of critical importance and were rigidly controlled. The method, which has been described in detail, proved to be satisfactory for the study of hyaluronidase production by various organisms and for the clinical investigation of antihyaluronidase. Antibody could be estimated only in fivefold serum increments, but this is not greatly inferior to the error inherent in most standard immunological procedures.

Earlier investigators were able to demonstrate hyaluronidase production by only a few types of Group A hemolytic streptococci. This was surprising in view of the fact that infection by other types is associated with the production of antihyaluronidase by infected human beings. More recent investigators have demonstrated that the enzyme is formed by many strains. These observations have been confirmed by the results of the present study. Thirty-one per cent of all strains of Group A hemolytic streptococci studied produced demonstrable hyaluronidase, usually in small amounts. Probably, if the experimental conditions could be improved, the frequency would be increased. This might be accomplished by the repeated transfer of the organism in a medium containing hyaluronic acid, since the presence of this substance has been stated to enhance the production of the enzyme and is presumably available in the infected animal. Strains of Groups C and G uniformly made hyaluronidase in very large amounts.

Evidence is presented, confirming the work of others, which demonstrates that Group A streptococcal antihyaluronidase is specific for the enzyme elaborated by organisms of this group, is heat-stable, and is not related to the nonspecific heat-labile inhibitors. There is every reason to believe that streptococcal antihyaluronidase is a true antibody. It exhibits specificity and heat stability and has been shown to be concentrated in the gamma globulin fraction of human sera.[19] In addition, it follows a general pattern typical of antibodies in that it is often present in the

19. Moore, D. H., and Harris, T. N.: Occurrence of Hyaluronidase Inhibitors in Fractions of Electrophoretically Separated Serum, J. Biol. Chem. **179**:377, 1949.

serum of newborn infants, disappears before the end of the first year, and reappears later in life as the direct result of infection by Group A hemolytic streptococci. Measurable antihyaluronidase is present in the serum of 70% of healthy young adults and in concentrations of 100 units or more in 35%.

The formation of streptococcal antihyaluronidase and antistreptolysin O was studied and compared in a group of infants and young children infected by Group A hemolytic streptococci. Antihyaluronidase was never produced when the antistreptolysin O response was absent or feeble, and rarely when the response was moderate and poorly sustained. Both antibodies were demonstrated in large amounts in the serum of subjects who were vigorous producers of antistreptolysin O. This information strongly indicates that hyaluronidase is a weaker antigen than streptolysin O. No specific relationship between the ability of the organism to produce hyaluronidase in vitro and the antibody response was demonstrated.

A previous report has described the antistreptolysin O response following Group A streptococcal infection in childhood. An increasingly vigorous production of this antibody was demonstrated with advancing age. Study of a small group of infants who suffered multiple streptococcal infections before the 30th month of age demonstrated an enhanced production of antibody with successive exposure to the Streptococcus. This suggested that conditioning of the antibody apparatus by successive infections was responsible for the changing patterns of antibody response rather than maturation of these organs with increasing age. A precisely similar sequence of events occurred in several of these children when antihyaluronidase was the antibody under study, and similar conclusions in regard to its formation may be drawn.

With these facts in mind, it was of interest to learn that the serum concentrations of antihyaluronidase were high early in the course of acute rheumatic fever in 14 of 17 cases. This suggested some intimate relationship between this antibody and the pathogenesis of the disease. The complete absence of antihyaluronidase over a long period in one case in which there were three streptococcal infections and two bouts of undoubted rheumatic fever clearly demonstrates that the pathological process is not dependent on the presence of this antibody. Others have previously made a similar observation.[16]

The high titers of antihyaluronidase in the other cases presumably are a reflection of the tendency of the rheumatic subject to form excessively large amounts of various antibodies which has been described by various authors.[20] This exaggerated antibody production probably results from a combination of factors, including intensive conditioning of the antibody apparatus by repeated streptococcal infections, exposure to strains of Streptococcus producing large amounts of the antigen, and inherent immunological hyperreactivity.[21] The last may be very important, and the whole abnormal immunological situation is probably related in some way to the pathogenesis of rheumatic fever.

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20. Rantz, L. A.; Randall, E., and Rantz, H. H.: Antistreptolysin O: A Study of This Antibody in Health and in Hemolytic Streptococcal Disease in Man, Am. J. Med. **5**:3, 1948. Anderson, H. C.; Kunkel, H. G., and McCarty, M.: Quantitative Antistreptokinase Studies in Patients Infected with Group A Hemolytic Streptococci: A Comparison with Serum Antistreptolysin and Gamma Globulin Levels with Special Reference to the Occurrence of Rheumatic Fever, J. Clin. Invest. **27**:425, 1948.

21. Creger, W. P.; Choy, S. H., and Rantz, L. A.: Experimental Determination of the Hypersensitive Diathesis in Man, J. Immunol. **66**:445, 1951.

The fact that the disease may appear in the complete absence of a demonstrable antihyaluronidase response probably indicates infection by an organism which is a feeble producer of hyaluronidase. A comparable situation has been demonstrated previously for the streptokinase-antistreptokinase system.[22]

In summary, this and previous work indicates that neither Group A streptococcal hyaluronidase nor its antibody, antihyaluronidase, plays an intimate role in the pathogenesis of rheumatic fever.

The possible role of hyaluronic acid, the substrate of the enzyme which is produced by many strains of these streptococci, remains unsettled. Strong hyaluronidase producers form relatively little of the polysaccharide,[12] and such strains have seemed to be nonrheumatogenic.[23] The suggestion could be made that streptococcal hyaluronic acid is essential to the rheumatic process, but no good evidence is yet available to support this view.

Many believe that the rheumatic process is the result of inappropriate immunological reactions involving some fraction or product of the hemolytic Streptococcus. Streptococcal hyaluronic acid has been reported to be nonantigenic,[24] but the definite possibility exists that antibody produced against this material is immediately absorbed onto the host-tissue hyaluronic acid. Preliminary attempts to detect such antibodies in this laboratory by passive transfer and complement fixation in the serum of persons convalescent from streptococcal infection or suffering from rheumatic fever have been without avail.

SUMMARY

A modification of the mucin-clot-prevention method for the measurement of streptococcal hyaluronidase and antihyaluronidase is described. Streptococcal antihyaluronidase was species- and group-specific and had the characteristics of a true antibody. Thirty-one per cent of 140 strains of Group A hemolytic streptococci produced hyaluronidase in vitro. Streptococcal antihyaluronidase appeared in the serum of infants and children following infection by Group A streptococci.

Streptococcal hyaluronidase is a weaker antigen than streptolysin O and is probably not formed in effective amounts by as many strains in vivo. Large amounts of streptococcal antihyaluronidase were present in the serum of nearly all subjects with active rheumatic fever but the disease may occur in its complete absence.

The streptococcal hyaluronidase-antihyaluronidase system is probably not intimately concerned in the pathogenesis of rheumatic fever. The possible role of streptococcal hyaluronic acid is unsettled.

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22. Rantz, L. A.; Boisvert, P. J., and Clark, W. H.: The Relationship of Serological Types of Group A Hemolytic Streptococci to Toxin Production and Antibody Response, Stanford M. Bull. **6**:55, 1948.

23. Kuttner, A. G., and Krumwiede, E.: Observations on the Effect of Streptococcal Upper Respiratory Infections on Rheumatic Children, J. Clin. Invest. **20**:273, 1941.

24. Seastone.[3] Kendall, F. E.; Heidelberger, M., and Dawson, M. H.: A Serologically Inactive Polysaccharide Elaborated by Mucoid Strains of Group A Hemolytic Streptococcus, J. Biol. Chem. **118**:61, 1937. Humphreys, J. H.: Antigenic Properties of Hyaluronic Acid, Biochem. J. **37**:460, 1943.

FURTHER OBSERVATIONS ON THE USE OF TRIETHYLENE MELAMINE IN NEOPLASTIC DISEASES

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IN A PREVIOUS paper[1] we reported that triethylene melamine, a substance which was developed for the crease-proofing of cloth, and which showed growth-inhibitory properties in tumors in animals, had beneficial effects in the treatment of 14 human beings suffering from lymphosarcoma, Hodgkin's disease, chronic myelogenous leukemia, fibrosarcoma, reticulum-cell sarcoma, and mycosis fungoides. We observed during that investigation no improvement in patients with anaplastic sarcoma, osteogenic sarcoma, and carcinoma. These findings have been substantially confirmed by the report of Karnofsky and associates.[2]

PRESENT STUDY

At this time we wish to report on the use of this chemotherapeutic agent in the treatment of an additional 28 adults with neoplastic diseases, and follow-up observations on 6 previously reported patients, who were still under study at the time of publication. Table 1 shows the classification and number of patients having each type of disease treated in the present and in the previously reported series, with the number of persons who showed improvement during treatment.

Of the 42 persons with neoplastic disease treated to date with triethylene melamine, 29 have died, 12 were still under study at the time of this report, and 1 was lost to the study. In the present series 21 patients have died. Of those previously reported on, eight died. Seven of the new and five of the previously described patients are still under study. Table 2 shows the disposition of the patients who received triethylene melamine therapy.

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1. Wright, L. T.; Wright, J. C.; Prigot, A., and Weintraub, S.: Remissions Caused by Tri-Ethylene Melamine in Certain Neoplastic Diseases, J. Nat. M. A. **42**:343-351 (Nov.) 1950.

2. Karnofsky, D. A.; Burchenal, J. H.; Armistead, G. C., Jr.; Southam, C. M.; Bernstein, J. L.; Craver, L. F., and Rhoads, C. P.: Triethylene Melamine in the Treatment of Neoplastic Disease, A. M. A. Arch. Int. Med. **87**:477-516 (April) 1951.

In the present series biopsy specimens of the tumors were taken, for both histological study and tissue culture with triethylene melamine, prior to the treatment of the patients with the drug. By employing this procedure, we were able to correlate closely our laboratory and clinical findings. We have noted that when triethylene melamine showed marked inhibition of the patient's tumor in tissue culture it exhibited similar marked inhibition of the tumor in vivo. Clearly evident, as well, was the fact that when slight inhibition of tumor growth in tissue culture was

TABLE 1.—*Classification of Patients Treated with Triethylene Melamine*

Diagnosis	Previously Reported	Present Series	Total	Number Improved
I. Sarcomas and Related Diseases				
Hodgkin's disease	2	4	6	4
Lymphosarcoma	3	0	3	3
Chronic lymphatic leukemia	0	3	3	3
Chronic myelogenous leukemia	1	0	1	1
Reticulum-cell sarcoma	1	2	3	2
Fibrosarcoma	1	3	4	4
Osteogenic sarcoma	1	1	2	0
Chondrosarcoma	0	1	1	0
Anaplastic sarcoma	1	0	1	0
Unclassified sarcoma	0	2	2	0
Multiple myeloma	0	3	3	0
Mycosis fungoides	1	0	1	1
II. Carcinomas				
Tonsil	1	0	1	0
Larynx	0	1	1	0
Lung	0	1	1	0
Esophagus	0	2	2	0
Stomach	0	1	1	0
Sigmoid	0	1	1	0
Kidney	0	1	1	0
Breast	0	1	1	0
Metastatic: primary site undetermined	2	1	3	0
Total	14	28	42	18

TABLE 2.—*Disposition of Patients Receiving Triethylene Melamine Therapy*

	Total Number Cases	Number Improved	Lost to Study	Number Died	Still Under Treatment
Previously reported	14	9	1	8	5
Present series	28	9	0	21	7
Total	42	18	1	29	12

produced by triethylene melamine slight inhibition occurred in the tumor of the patient under treatment.[3]

Triethylene melamine [4] was administered orally to a series of 42 patients, either in doses of 5 or 10 mg. daily in courses of 1 to 4 days or in the dosage of 1 mg. daily in courses of 5 to 15 days. The average dose provided per course was 5 mg. daily for 3 days. The total dosage per course varied from 5 to 30 mg. The maximum total

3. Antikajian, G.; Wright, L. T.; Plummer, J. I., and Weintraub, S.: The Effect of Triethylene Melamine, Aureomycin, and Some 4-Amino Derivatives of Folic Acid on Tissues in Vitro, to be published. Plummer, J. I.: Personal communication to the authors.

4. Triethylene melamine was furnished through the courtesy of the Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

dosage given to date to a single patient was 120 mg. in 168 days. When an initial course of 15 to 20 mg. produced no therapeutic effect after 15 days, and when the patient was free of toxic effects, a repeat course was given. Thereafter, courses generally were repeated at monthly intervals when deemed necessary. The older patients became toxic more rapidly than did the younger patients. For this reason smaller dosages were used for the older patients. Fifty milligrams of pyridoxine administered orally simultaneously with the triethylene melamine so significantly decreased the incidence of nausea and vomiting, which occurred in some instances following the administration of triethylene melamine, that we now routinely use this procedure.

RESULTS

Improvement was observed in 18 of the 42 patients treated with triethylene melamine, in 9 of the present series, and in 9 of the previous series. Four of the six persons with Hodgkin's disease, the three with lymphosarcoma, two of the three with reticulum-cell sarcoma, the three with chronic lymphatic leukemia, the four with fibrosarcoma, the one having chronic myelogenous leukemia, and the one with mycosis fungoides showed definite improvement with therapy. One patient with multiple myeloma, who has received 70 mg. of triethylene melamine, and who has been under study 181 days to date, has shown no significant change in the clinical condition or laboratory findings at the time of this report. No beneficial results were demonstrated in 23 patients: 2 with Hodgkin's disease, 1 with anaplastic sarcoma, 2 with osteogenic sarcoma, 1 with chrondrosarcoma, 1 with reticulum-cell sarcoma, 2 with unclassified sarcomas, 2 with multiple myelomas, and 12 with carcinomas. Table 3 presents a summary of the treatment of the 42 patients.

Lymphosarcoma.—Three patients with lymphosarcoma are still under study and treatment with triethylene melamine. Under observation all three showed improvement, as manifested by definite decreases in the size of the enlarged nodes and masses. The first patient (Case 34) showed a progressive decrease in the size of enlarged submaxillary, cervical, and axillary lymph nodes, associated with improvement in the general condition. This improvement, after it was first noted, lasted 89 days before relapse occurred after the first course of the drug and 14 days after the second course. The second patient having lymphosarcoma (Case 41) in whom improvement was observed showed a moderate decrease in the size of all enlarged nodes and masses after each course of treatment with triethylene melamine, associated with slight general improvement. Tissue culture of this patient's tumor revealed only moderate inhibition with triethylene melamine, which corresponded to the clinical observations. The third patient with lymphosarcoma treated with triethylene melamine is described in detail.

CASE 37.—A 51-year-old man was admitted to Harlem Hospital on Oct. 1, 1948, because of a large, painless mass in the left cervical region, which appeared 15 months prior to admission and subsequently had increased slowly in size.

Work-up on admission revealed a large, firm, nodular mass in the left supraclavicular fossa, hypertension, a dilatation of the ascending aorta, and a large left ventricle.

Between Oct. 15, 1948, and June 8, 1950, the patient was treated with several of the folic acid antagonists. During this period large nodes developed in the right supraclavicular fossa and in both axillae. While he was under treatment with the folic acid antagonists, several temporary slight decreases occurred in the size of the nodes.

TABLE 3.—*General Summary of Treatment of Forty-Two Patients with Neoplastic Diseases Given Triethylene Melamine Orally*

Case No.	Age; Sex	Diagnosis	Oral Treatment with Triethylene Melamine, Courses; Days; Total Dosage	Clinical Response	First Evidence of Improvement and Duration	Days from Initial Dose Until Death
1	53 F	Fibrosarcoma	5 mg. a day; 3 days: 7/14/50-7/16/50; total, 15 mg.	Marked and sudden decrease in size of abdominal mass without increase in pain; no change in numerous scattered subcutaneous metastases	8th day; duration, 1 day (died)	9
2	50 M	Reticulum-cell sarcoma	5 mg. a day; 3 days: 7/16/50-7/18/50; total, 15 mg.	Decrease in size of liver from 3 finger-breadths below costal margin to normal; no appreciable change in size of cervical nodes	6th day (died a few hours after improvement first noted)	6
3	61 F	Anaplastic sarcoma	5 mg. a day; 3 days: 5/23/50-5/25/50 10 mg. a day; 2 days: 6/9/50-6/10/50 Total, 35 mg.	No improvement; all masses increased progressively in size	....	34
4	20 M	Osteogenic sarcoma	10 mg.; 1 day: 6/1/50 5 mg. a day; 4 days: 6/9/50-6/12/50 10 mg.; 1 day: 6/16/50 10 mg. a day; 3 days: 6/24/50-6/26/50 Total, 70 mg.	No improvement; metastases increased in size and extent; condition went progressively downhill; patient died	....	42
5	47 M	Mycosis fungoides	10 mg. a day; 2 days: 6/2/50-6/3/50 10 mg. a day; 2 days: 6/19/50-6/20/50 Total, 40 mg.	Progressive drying and decrease in size of tumorous lesions after both courses; more marked after 2d course; died	1st course: 4th day; duration, 7 days 2d course: 8th day; duration, 4 days (died)	31
6	74 M	Metastatic carcinoma to ribs	10 mg. a day; 2 days: 6/2/50-6/3/50 5 mg. a day; 4 days: 6/16/50-6/19/50 Total, 40 mg.	No improvement; died suddenly	....	33
7	71 M	Carcinoma of tonsil	5 mg. a day; 3 days: 5/23/50-5/25/50 10 mg. a day; 3 days: 6/2/50-6/4/50 5 mg. a day; 2 days: 6/15/50-6/16/50 Total, 55 mg.	No improvement; after first 2 courses tonsillar mass became temporarily more edematous and hyperemic	....	38
8	62 F	Metastatic carcinoma: primary site undetermined	5 mg. a day; 3 days: 5/23/50-5/25/50; total, 15 mg.	No improvement; abdominal metastases increased in size; condition went progressively downhill; patient died	....	25
9	51 F	Carcinoma of breast	10 mg. a day; 2 days: 10/27/50-10/28/50; total, 15 mg.	No improvement; dyspnea increased; condition went progressively downhill	....	27
10	43 F	Hodgkin's disease	5 mg.; 1 day: 10/11/50; total, 5 mg.	No improvement; died afternoon after first dose	....	Few hours
11	16 M	Reticulum-cell sarcoma	10 mg. a day; 2 days: 9/6/50-9/7/50; total, 20 mg.	General improvement and decrease of elevated temperature to normal 5 days after 1st dose; marked decrease in size of mediastinal nodes, but no apparent change in small cervical nodes noted 2 days later; fever recurred; condition went downhill; patient died	5th day; duration, 5 days	13
12	53 M	Hodgkin's disease	5 mg. a day; 3 days: 9/22/50-9/24/50 5 mg. a day; 3 days: 10/16/50-10/18/50 5 mg. a day; 3 days: 11/14/50-11/16/50 Total, 45 mg.	Temporary decrease in size of all enlarged lymph nodes and liver with associated general improvement after each course; temporary decrease in elevated temperature to normal after 1st course; uremia, recurrent fever developed; patient suddenly died	1st course: 6th day; duration, 20 days 2d course: 14th day; duration, 8 days 3d course: 6th day; duration, 5 days	64
13	56 M	Metastatic carcinoma: primary site undetermined	5 mg. a day; 3 days: 10/19/50-10/21/50 5 mg. a day; 3 days: 11/7/50-11/9/50 Total, 30 mg.	No improvement; progressive increase in size of skin metastases; bone metastases developed as shown by roentgenogram during treatment; progressive downhill course; died	....	31

TABLE 3.—*General Summary of Treatment of Forty-Two Patients with Neoplastic Diseases Given Triethylene Melamine Orally—Continued*

Case No.	Age; Sex	Diagnosis	Oral Treatment with Triethylene Melamine, Courses; Days; Total Dosage	Clinical Response	First Evidence of Improvement and Duration	Days from Initial Dose Until Death
14	59 M	Carcinoma of larynx	5 mg. a day; 3 days: 10/19/50-10/21/50 5 mg. a day; 2 days: 11/4/50-11/5/50 Total, 25 mg.	Questionable temporary slight decrease in size of metastases in neck after each course	1st course: 5th day; duration, 12 days 2d course: 2d day; duration, 24 days	66
15	70 F	Osteogenic sarcoma	1 mg. a day; 15 days: 1/6/51-1/21/51; total, 15 mg.	No improvement; progressive increase in lung metastases; no roentgen change in bone lesion; progressive downhill course; died	....	34
16	58 F	Chronic lymphatic leukemia and carcinoma of cervix	5 mg. a day; 3 days: 12/15/50-12/17/50; total, 15 mg.	Progressive decrease in total W.B.C.; no change in nodes, abdominal mass, or cervical lesion; died 6 days after onset of therapy	3d day; duration, 3 days	6
17	20 M	Chondrosarcoma	10 mg. a day; 2 days: 12/30/50-12/31/50; total, 20 mg.	No improvement; downhill course; died	....	3
18	68 M	Sarcoma, type undetermined	5 mg. a day; 3 days: 10/27/50-10/29/50 5 mg. a day; 3 days: 12/1/50-12/3/50 Total, 30 mg.	No improvement; ascites and increased peripheral edema developed; patient died	....	46
19	40 M	Multiple myeloma	5 mg. a day; 3 days: 9/9/50-9/11/50; total, 15 mg.	No improvement; uremia, weakness, and marked anemia developed; patient died	....	10
20	52 F	Carcinoma of stomach	5 mg. a day; 3 days: 10/20/50-10/22/50 5 mg. a day; 2 days: 11/4/50-11/5/50 Total, 25 mg.	Questionable decrease in size and softening of abdominal mass	3d day; duration, 9 days	19
21	63 M	Multiple myeloma	5 mg. a day; 3 days: 9/8/50-9/10/50; total, 15 mg.	No improvement; patient's condition remained terminal; died 3 days after onset of therapy	....	3
22	47 M	Carcinoma of kidney	5 mg. a day; 3 days: 11/25/50-11/27/50 5 mg. a day; 3 days: 12/8/50-12/10/50 Total, 30 mg.	No improvement; metastases to skin increased in size and number; progressive downhill course; died	....	20
23	47 M	Sarcoma, type undetermined	5 mg. a day; 3 days: 8/5/50-8/7/50; total, 15 mg.	No improvement; condition remained poor; patient died suddenly 4 days after onset of therapy	....	4
24	46 M	Carcinoma of lung	5 mg. a day; 3 days: 12/29/50-12/31/50 5 mg. a day; 3 days: 1/17/51-1/19/51 Total, 30 mg.	No improvement; progressive and rapid downhill course; skin lesions and apparently brain metastases increased in size	....	33
25	60(?) F	Reticulum-cell sarcoma	5 mg. a day; 3 days: 9/1/50-9/3/50 5 mg. a day; 2 days: 9/23/50-9/24/50 5 mg.; 1 day: 9/26/50 Total, 30 mg.	After 1st course temporary decrease in size of cervical masses was noted; general condition deteriorated; died	1st course: 12th day; duration, 4 days	23
26	39 F	Carcinoma of sigmoid	10 mg. a day; 2 days: 9/29/50-9/30/50 10 mg. a day; 2 days: 10/20/50-10/21/50 Total, 40 mg.	No improvement; abdominal mass increased in size; pressure symptoms increased	....	52
27	59 M	Carcinoma of esophagus	5 mg. a day; 3 days: 9/12/50-9/14/50 5 mg. a day; 3 days: 10/12/50-10/14/50 Total, 30 mg.	No improvement; condition remained fair throughout therapy; patient suddenly died	....	35
28	56 M	Fibrosarcoma	5 mg. a day; 3 days: 9/22/50-9/24/50 5 mg. a day; 3 days: 10/17/50-10/19/50 5 mg. a day; 3 days: 11/21/50-11/23/50 Total, 45 mg.	Decrease in size of abdominal mass and subcutaneous mass, associated with general improvement and increased appetite; although masses continued to decrease in size, patient became weaker; condition went downhill; patient died	1st course: 10th day; duration, 53 days	63
29	73 F	Hodgkin's disease	5 mg. a day; 3 days: 7/7/50-7/9/50 5 mg. a day; 2 days: 8/11/50-8/12/50 Total, 25 mg.	Enlarged submaxillary nodes decreased progressively in size with associated general improvement; 24 days after 2d course, nodes again began to increase in size; patient refused to reenter the hospital for repeat biopsy and further medication; lost to study after 118 days	....	..

TABLE 3.—*General Summary of Treatment of Forty-Two Patients with Neoplastic Diseases Given Triethylene Melamine Orally—Continued*

Case No.	Age: Sex	Diagnosis	Oral Treatment with Triethylene Melamine, Courses; Days; Total Dosage	Clinical Response	First Evidence of Improvement and Duration	Days from Initial Dose Until Death
30	56 F	Carcinoma of esophagus	5 mg. a day; 3 days: 8/2/50-8/4/50 5 mg. a day; 3 days: 9/1/50-9/3/50 5 mg. a day; 3 days: 10/7/50-10/9/50 5 mg. a day; 3 days: 11/16/50-11/18/50 Total, 60 mg.	No improvement; no apparent change during treatment; changed to another form of chemotherapy; still under study after 236 days	....	..
31	19 M	Hodgkin's disease	5 mg. a day; 2 days: 2/1/51-2/2/51; total, 10 mg.	Questionable improvement noted; patient started taking brewers' yeast at the same time triethylene melamine therapy was initiated; general improvement was decrease in fatigue noted 8 days later; questionable decrease observed in size of slightly enlarged cervical nodes; still under study after 54 days	8th day; duration, 43 days to date	..
32	47 M	Fibrosarcoma	10 mg. a day; 2 days: 10/6/50-10/7/50 5 mg. a day; 3 days: 10/24/50-10/26/50 5 mg. a day; 3 days: 11/21/50-11/23/50 2.5 mg. a day; 4 days: 12/15/50-12/18/50 5 mg. a day; 3 days: 1/4/51-1/6/51 5 mg. a day; 3 days: 1/23/51-1/25/51 5 mg. a day; 3 days: 2/17/51-2/19/51 5 mg. a day; 3 days: 3/15/51-3/17/51 Total, 120 mg.	Moderate temporary decrease of 1.5 to 3 cm. in size of enlarged liver, associated with decrease of abdominal distention, improved appetite, and general improvement, noted after 1st, 2d, 3d, 4th, 5th, and 7th courses; since the 8th course slowly downhill condition, with increased weakness, anorexia, dyspnea, and ascites; still under study after 168 days	1st course: 17th day 2d course: 8th day; duration, 57 days 3d course: 14th day; duration, 7 days 4th course: 13th day; duration, 5 days 5th course: 4th day; duration, 14 days 7th course: 7th day; duration, 10 days	..
33	59 F	Fibrosarcoma	5 mg. a day; 3 days: 1/9/51-1/11/51 5 mg. a day; 3 days: 1/26/51-1/28/51 5 mg. a day; 2 days: 3/8/51-3/9/51 Total, 40 mg.	Moderate temporary decrease in size of pelvic mass; moderate decrease in pain and pressure symptoms from mass and general improvement after first 2 courses; still under study after 76 days	1st course: 8th day 2d course: 14th day; duration, 50 days to date	..
34	29 F	Lymphosarcoma and lupus erythematosus	10 mg. a day; 2 days: 7/22/50-7/23/50 5 mg. a day; 3 days: 10/20/50-10/22/50 Total, 35 mg.	Temporary decrease in size of submaxillary, cervical, and axillary nodes, associated with pain, after each course; still under study after 224 days	1st course: 5th day; duration, 89 days 2d course: 6th day; duration, 14 days	..
35	77 F	Chronic lymphatic leukemia	5 mg. a day; 3 days: 3/10/51-3/12/51; total, 15 mg.	Progressive decrease in total W.B.C. but no change in differential count to date; no change in size of nodes; patient feels generally better but is still weak and anorectic; still under study after 16 days	3d day; duration, 13 days to date	..
36	48 M	Multiple myeloma	5 mg. a day; 2 days: 10/27/50-10/28/50 5 mg. a day; 3 days: 11/16/50-11/18/50 5 mg. a day; 3 days: 12/8/50-12/10/50 5 mg. a day; 3 days: 1/26/51-1/28/51 5 mg. a day; 3 days: 2/22/51-2/24/51 Total, 70 mg.	No improvement; no change in general condition or roentgenograms of bones; just prior to 5th course, patient had pain in spine at C-7 which has persisted; still under study after 181 days	....	..
37	51 M	Lymphosarcoma	10 mg. a day; 2 days: 6/13/50-6/14/50 10 mg. a day; 2 days: 6/29/50-6/30/50 5 mg.; 1 day: 7/1/50 10 mg. a day; 2 days: 8/18/50-8/19/50 Total, 65 mg.	Painless progressive, marked decrease in size of all enlarged cervical and axillary nodes, with associated general improvement; by 9/7/50, all nodes had decreased markedly in size and were barely palpable; general condition good; improvement has been maintained to date; still under study after 256 days	1st course: 7th day; duration, 249 days; maximum improvement for 162 days with complete remission to date: 3/26/51	..

TABLE 3.—*General Summary of Treatment of Forty-Two Patients with Neoplastic Diseases Given Triethylene Melamine Orally—Continued*

Case No.	Age; Sex	Diagnosis	Oral Treatment with Triethylene Melamine, Courses; Days; Total Dosage	Clinical Response	First Evidence of Improvement and Duration	Days from Initial Dose Until Death
38	49 M	Chronic lymphatic leukemia	10 mg. a day; 2 days: 9/28/50-9/29/50 10 mg. a day; 2 days: 10/21/50-10/22/50 5 mg. a day; 3 days: 12/1/50-12/3/50 5 mg.; 1 day: 2/9/51 Total, 60 mg.	No clinical or significant hematological improvement noted after 1st course; after 2d and 3d courses, marked decrease in the size of cervical and axillary nodes, moderate decrease in size of liver were noted; total W.B.C. decreased to normal; differential count improved to almost normal; still under study after 179 days	2d course: 26th day 3d course: 14th day; duration, 131 days to date: 3/26/51	..
39	40 F	Chronic myelogenous leukemia	10 mg. a day; 2 days: 7/13/50-7/14/50 10 mg.; 1 day: 8/11/50 5 mg. a day; 3 days: 8/23/50-8/25/50 5 mg. a day; 3 days: 9/20/50-9/22/50 5 mg. a day; 3 days: 10/20/50-10/22/50 5 mg. a day; 3 days: 12/1/50-12/3/50 Total, 90 mg.	Decrease in enlarged spleen to normal size; disappearance of left flank pain; Decrease in enlarged spleen to normal change in both differential count and bone marrow count to normal, with associated general improvement; this complete remission has lasted 95 days to date; still under study after 256 days	1st course: 5th day 3d course: 8th day 4th course: no check-up until 27th day; duration, 10 days 5th course: 19th day; duration, 10 days 6th course: 21st day; duration, 95 days	..
40	44 M	Hodgkin's disease	5 mg. a day; 3 days: 1/26/51-1/28/51 5 mg. a day; 2 days: 2/9/51-2/10/51 1 mg. a day; 15 days: 3/16/51-3/30/51 Total, 40 mg. "Leucovorin": 3 mg. a day intramuscularly: 3/7/51-3/26/51	After the first 2 courses, elevated temperature persisted, nodes increased in size; after 3d course, temperature decreased to normal and nodes decreased in size; general condition remained poor; patient died; while receiving "leucovorin" W.B.C. which had been low increased from 2,300 to normal	3d course: 21st day; duration, 5 days (died)	74
41	49 M	Lymphosarcoma	10 mg. a day; 2 days: 6/14/50-6/15/50 5 mg. a day; 3 days: 8/11/50-8/13/50 5 mg. a day; 3 days: 9/23/50-9/25/50 1 mg. a day; 15 days: 1/19/51-2/2/51 Total, 65 mg. "Leucovorin": 3 mg. a day intramuscularly: 2/16/51-2/28/51; 3/14/51-3/26/51	Moderate decrease in size of enlarged nodes and masses after each course of triethylene melamine; "leucovorin" increased W.B.C. from 3,700 on 2/16/51 to 4,700 in 12 days; "leucovorin" discontinued; W.B.C. decreased to 2,800 in 14 days; when drug again given, W.B.C. increased to 5,250 in 5 days; still under treatment after 285 days	1st course: 37th day; duration, 21 days 2d course: 5th day; duration, 5 days 3d course: 23d day; duration, 5 days 4th course: 4th day; duration, 38 days	..
42	28 M	Hodgkin's disease	10 mg. a day; 2 days: 6/15/50-6/16/50 10 mg. a day; 2 days: 6/27/50-6/28/50 5 mg.; 1 day: 6/29/50 5 mg. a day; 3 days: 7/28/50-7/30/50 5 mg. a day; 3 days: 9/22/50-9/24/50 5 mg. a day; 3 days: 10/27/50-10/29/50 5 mg. a day; 3 days: 12/15/50-12/17/50 5 mg. a day; 2 days: 1/19/51-1/20/51 Total, 115 mg.	After each course decreases occurred in size of all enlarged cervical, axillary, and hilar nodes, with associated general improvement and slight gain in weight; still under study after 286 days	2d course: 10th day; duration, 23 days 3d course: 13th day; duration, 42 days 4th course: 6th day; duration, 28 days 5th course: 6th day; duration, 35 days 6th course: 6th day; duration, 28 days 7th course: 6th day; duration, 56 days	..

A tissue culture of one of the patient's nodes with triethylene melamine showed marked inhibition of growth. On June 13, 1950, triethylene melamine therapy was started, with 10 mg. of the drug administered daily for two days. On June 29 the second course was started—10 mg.

Fig. 1 (Case 37).—Photograph of a patient with lymphosarcoma previously reported on, taken on Jan. 19, 1950, before treatment with triethylene melamine.

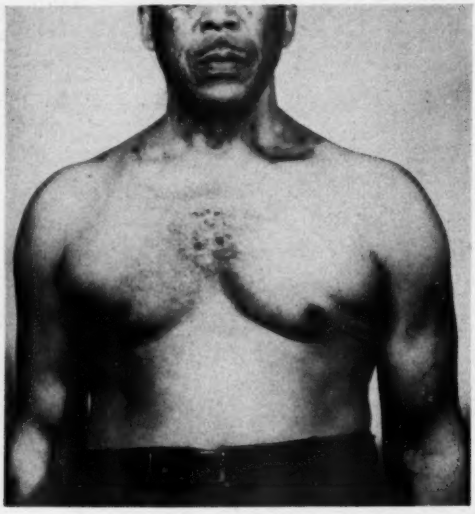

Fig. 2 (Case 37).—Same patient photographed on May 17, 1951. This patient has required no medication since last course of triethylene melamine therapy on Aug. 19, 1950.

daily for two days and 5 mg. on the third day. Beginning Aug. 18, 1950, 10 mg. was administered for two days. Seven days following the first course of therapy, a decrease was observed in the size of all enlarged cervical and axillary nodes. The enlarged nodes continued to decrease

progressively until Sept. 7, 1950, at which time they were barely palpable. There was a marked improvement in the patient's general condition, and he stated that he felt better than he had at any time in the last three years. This remission had continued for 162 days at the time of this report. Figures 1 and 2 show this patient before and after treatment.

A lymph node biopsy specimen taken after triethylene melamine treatment showed fibrosis and hyaline degeneration. Figures 3 and 4 are of lymph node biopsy specimens before and after treatment.

The toxic manifestations noted during the treatment of this patient consisted of diarrhea on the fourth and fifth days after the first course and sudden weakness on the second and third

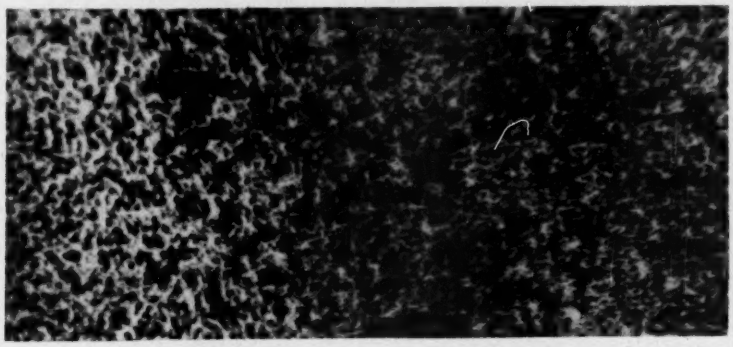

Fig. 3 (Case 37).—Photomicrograph of node from patient with lymphosarcoma before treatment with triethylene melamine.

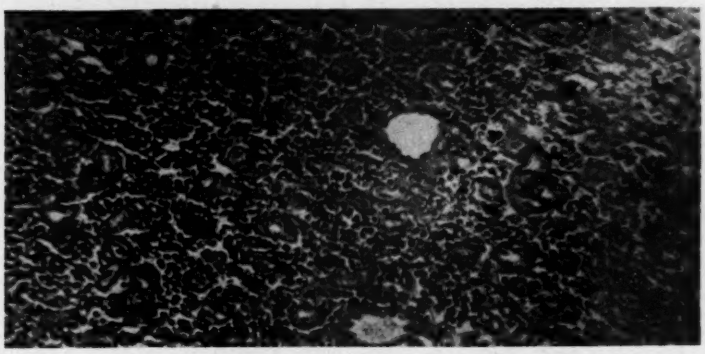

Fig. 4 (Case 37).—Photomicrograph of node from the same patient, showing fibrosis and hyaline degeneration, one month after treatment with triethylene melamine.

days after the third course. A moderate decrease in the total white blood cell count occurred 9 days after the second course and 11 days after the third course.

Hodgkin's Disease.—There was improvement with triethylene melamine therapy in four patients with Hodgkin's disease. This improvement consisted of decreases in the size of the enlarged nodes, with associated general improvement, and, in two cases, of a reduction of the fever which had been present at initiation of treatment. The first patient (Case 12) had generalized lymphadenopathy, hepatomegaly, and fever and was in poor condition. During treatment there was a temporary reduction

in the elevated temperature and in the size of the enlarged nodes and liver, with associated general improvement. Fifty-four days after the beginning of medication, the blood urea nitrogen rose from 7.5 to 60 mg., and microscopic red blood cells appeared in the urine. The patient died suddenly when he had been under study 64 days. The second patient (Case 29) showed a decrease in the size of the enlarged nodes after each of two courses of the drug. This patient was under observation 118 days and was then lost to study. The third patient (Case 40), to whom 40 mg. of triethylene melamine was given in three courses, was in poor condition, with fever, anemia, generalized lymphadenopathy, skin rash, and pruritus when treatment was instituted. There was no improvement until the third course of treatment with the drug, when a marked decrease occurred in the size of the nodes, as well as a return of the temperature to normal. Five days later the patient died suddenly, after being under study 74 days. The fourth patient with Hodgkin's disease is described below.

CASE 42.—A 28-year-old man was admitted to the cancer research service on Dec. 8, 1949, after a biopsy at another hospital which revealed Hodgkin's disease. The patient reported a three-month history of enlarged nodes in the right cervical area which had increased progressively in size.

Examination revealed enlarged nodes on the right side in the supraclavicular area, neck, axilla, and hilar region.

Between Dec. 15, 1949, and May 15, 1950, the patient received first an antibiotic and then "a-methopterin" (4-amino-10-N-methylpteroylglutamic acid). With "a-methopterin" therapy there was some slight temporary decrease in the size of the enlarged nodes.

Inhibition of growth was demonstrated with triethylene melamine in tissue cultures of one of the nodes taken from this patient. Triethylene melamine therapy was instituted on June 15, 1950, and seven courses of the drug had been administered in 286 days, to the time of this report. Details of these courses are shown in Table 3.

Between the 6th and 10th days following each of the last six courses of the drug, there was a reduction in the size of the enlarged cervical, axillary, and hilar nodes, associated with a slight increase in weight and general improvement. No change was seen after the first course. The patient stated that since the institution of this treament he felt generally better than at any time in the previous year. The remissions following the last six courses of the drug were 23, 42, 28, 35, 28, and 56 days, respectively. Figures 5 and 6 show the patient before and after treatment.

The toxic reactions which occurred in this patient during treatment were as follows: Nausea and vomiting were present from 10 hours to six days after the first, fifth, and seventh courses; red blood cells were temporarily found in the urine after the fourth and sixth courses, and temporary decreases in the total white blood cell count occurred after the second, fifth, and sixth courses.

Fibrosarcoma.—Improvement was noted in four patients with fibrosarcoma and consisted of a decrease in the size of the masses present on initiation of treatment. In these patients only moderate and temporary improvement occurred. One patient (Case 1) showed a marked and sudden decrease in the size of an abdominal mass but no change in subcutaneous metastatic nodules. This patient, who was moribund at onset of therapy, died nine days after a 15-mg. course of drug therapy. The second patient (Case 28) showed progressive, slow decreases in the size of a mass in the right upper abdominal quadrant and a subcutaneous mass on the left arm 10 days after the first course of treatment with the drug. Two further courses were administered; in spite of the decrease in the size of the tumors, the patient's condition went slowly downhill, and he died after 63 days of study. The third patient (Case 32) is still under study at the time of this report and has received a total of 120 mg. of tri-

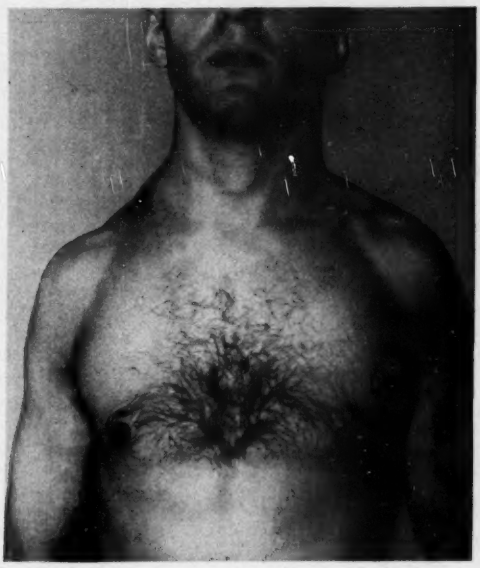

Fig. 5 (Case 42).—Photograph of a patient with Hodgkin's disease previously reported on, taken on Jan. 19, 1950, before treatment with triethylene melamine.

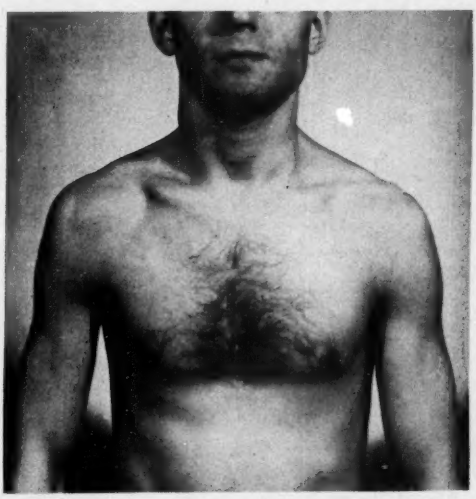

Fig. 6 (Case 42).—Same patient photographed on May 17, 1951, 11 months after initiation of treatment with triethylene melamine.

ethylene melamine in eight courses over 168 days. After each, but one of the courses, a temporary decrease occurred in the size of the masses in the epigastrium and right upper abdominal quadrant. The fourth patient having fibrosarcoma (Case 33), still under treatment, also had a slight temporary decrease in the size of a large pelvic mass, associated with some relief of pain and decrease in the pressure symptoms from the mass.

Reticulum-Cell Sarcoma.—Two patients with reticulum-cell sarcoma showed temporary decreases in the size of tumorous masses after triethylene melamine therapy. In the first patient (Case 2) the enlarged liver was reduced to normal size

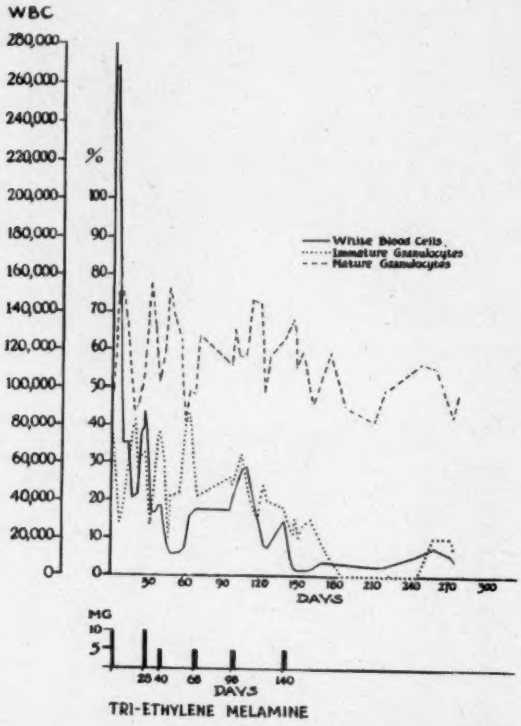

Fig. 7 (Case 39).—Chart showing effect of triethylene melamine administration on white blood cells.

in six days after a 15-mg. course of treatment with the drug, at which time the patient suddenly died. A patient with generalized adenopathy and fever (Case 11) showed a reduction in the temperature to normal and marked decrease in the size of mediastinal nodes. This patient's condition remained improved for five days, at which time a recurrence of the initial symptoms developed, and he died 13 days after initiation of treatment.

Myelogenous Leukemia.—The condition of one patient with chronic myelogenous leukemia, treated with triethylene melamine, went into a complete remission. This case is presented in detail.

CASE 39.—A 40-year-old woman was first admitted to Harlem Hospital on Nov. 4, 1948, with a history of three weeks of shortness of breath, palpitations, and the presence of a firm mass in the left upper abdomen. Results of physical examination were normal except for an enlarged spleen. Hematological work-up confirmed the diagnosis of chronic myelogenous leukemia.

On Nov. 12 treatment was started with the folic acid antagonists, and this medication was continued until June 15, 1950. During this period there was a temporary hematological and clinical improvement, followed by a relapse.

Triethylene melamine therapy was instituted on July 13, 1950. Six courses have been administered to the time of this report, as shown in Table 3.

A total of 90 mg. has been administered to date in 256 days.

Prior to this medication, the patient's spleen extended down to the left iliac crest, and she complained of fairly constant left flank pain. The total white blood cell count was 266,000, with 48.5% mature granulocytes, 40% immature granulocytes, and 3% lymphocytes. After each course of triethylene melamine therapy, the total white blood cell count decreased and the differential count and bone marrow smears progressively improved. The spleen decreased in size, and the left flank pain subsided. By Dec. 28, 1950, the spleen was no longer palpable, the white blood cell count, differential count, and the bone marrow smear were normal. This complete remission has lasted 82 days to date. Figure 7 shows the changes which occurred in the total white blood cell count and differential count while she received triethylene melamine.

Drug toxicity in this case was manifested by nausea on the second day of the first course and episodes of sudden weakness occurring on the second to fifth days of the first, fourth, fifth, and sixth courses.

Chronic Lymphatic Leukemia.—Three patients with chronic lymphatic leukemia have been treated with triethylene melamine, with improvement. One patient (Case 16) was moribund at the onset of treatment and had an associated far-advanced carcinoma of the cervix. After one course of treatment with the drug, there was a progressive decrease in the total white blood cell count, but no change in the differential count or clinical condition occurred. This patient died six days after institution of treatment. The second patient (Case 35) had been under study for 16 days at the time of this report, and there was a progressive decrease in the total white blood cell count. There were no changes in the differential picture or in the size of the enlarged lymph nodes. Associated with the decrease in the white blood cell count, there was considerable general improvement. The third patient with chronic lymphatic leukemia treated with triethylene melamine is described in detail.

CASE 38.—A 49-year-old man was admitted to Harlem Hospital on Sept. 22, 1950, with a three-month history of progressive painless swelling of nodes in the neck and under the arm and a cough of one month's duration, productive of a few teaspoons of white phlegm each day.

Physical examination revealed a fairly well-nourished man with numerous enlarged cervical, axillary, and inguinal nodes, enlargement of the liver to 2½ fingerbreadths below the costal margin, and enlargement of the spleen to 3½ fingerbreadths below the costal margin. Hematological work-up revealed chronic lymphatic leukemia.

Tissue culture of a node with triethylene melamine showed marked inhibition of growth, and subsequently treatment with triethylene melamine was started on Sept. 28, 1950. He received four courses of the therapy as shown in Table 3.

A total of 60 mg. of the drug was administered to date in 179 days.

After the first course of triethylene melamine therapy, a decrease was noted in the total white blood cell count, but no essential change occurred in the differential count or in the clinical picture. Twenty-six days after the second course, the enlarged nodes, liver, and spleen decreased in size. At this time the patient stated that he was able to wear and fasten smaller collars than before. The white blood cell count coincidentally decreased to normal, and the differential count improved. Further decrease in the nodes and liver occurred, and the hematological picture returned to normal after the third course of treatment with the drug.

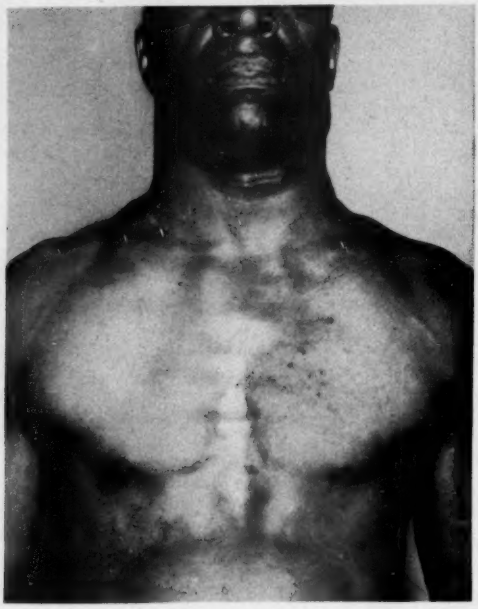

Fig. 8 (Case 38).—Photograph of patient with chronic lymphatic leukemia taken on Sept. 28, 1950, before treatment with triethylene melamine.

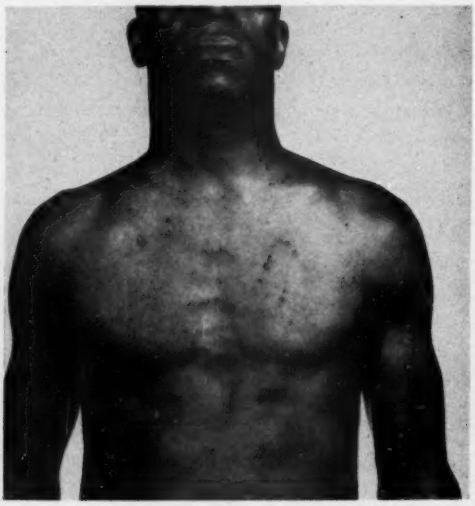

Fig. 9 (Case 38).—Same patient photographed on Jan. 4, 1951, 14 weeks after initiation of treatment with triethylene melamine. Note reduction in size of lymph nodes. At time of this photograph, patient's lymphocyte count was within normal limits.

A single dose of 5 mg. was given to decrease the size of the nodes and spleen further, without decreasing the total white blood cell count, but no further significant change occurred. Figures 8 and 9 show the patient before and after triethylene melamine therapy. Figure 10 shows the course of the white blood cell count and lymphocytes during treatment.

Mycosis Fungoides.—One patient with mycosis fungoides (Case 5) responded to triethylene melamine treatment by demonstrating marked decrease in the size of the tumorous lesions and drying of skin lesions. This patient died suddenly after 31 days of study.

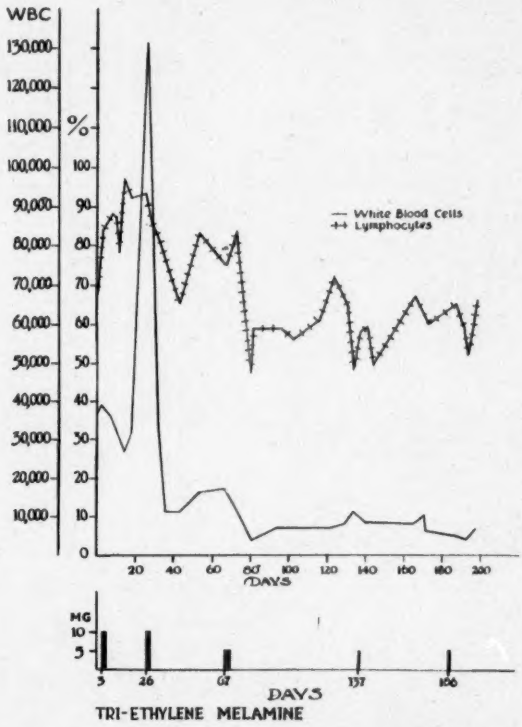

Fig. 10 (Case 38).—Chart showing effect of triethylene melamine administration on white blood cells.

TOXIC MANIFESTATIONS

Toxic manifestations during treatment with triethylene melamine were both immediate and delayed. The immediate effects consisted of nausea, vomiting, and diarrhea. With the simultaneous administration of pyridoxine, nausea and vomiting rarely occurred. The delayed toxic reactions observed were temporary decreases in the total white blood cell count, weakness, temporary increases in the blood urea nitrogen, and the transient appearance of microscopic red blood cells in the urine. When triethylene melamine was administered in a dosage of 1 mg. daily for 15 days, instead of 5 mg. daily for three days, none of the immediate toxic effects of

TABLE 4.—*Incidence of Toxic Manifestations in Thirty-Three of Forty-Two Patients Given Oral Treatment with Triethylene Melamine*

Case No.	Nausea, Vomiting, Diarrhea	Weakness	Temporary Increase in Urea Nitrogen, Mg./100 Cc.	Transient Incidence of R.B.C. in Urine	Temporary Decrease in W.B.C./Cu. Mm. Below Normal Range
1	.....	6th to 9th day	.....	.....	6,600 to 3,350
4	1st course: nausea and vomiting 1st day; 12th to 27th hr.	.....	.....	.....	.....
5	1st course: nausea and vomiting 20th hr. to 13th day; diarrhea 20th hr. to 4th day 2d course: diarrhea 12th hr. to 3d day	2d course: 8th to 12th day	1st course: 28th day, 11.46 to 22.44	.....	1st course: 12,500 to 4,750 2d course: 5,100 to 1,050
6	.....	1st course: 5th to 11th day	.....	.....	1st course: 6,700 to 1,900 2d course: 11,800 to 2,600
7	.....	.....	.....	.....	3d course: 11,250 to 1,250
8	.....	.....	.....	.....	10,050 to 1,050
9	Nausea 4th day (pyridoxine)	.....	.....	.....	5,800 to 2,100
11	Nausea and vomiting 10th day (pyridoxine)	.....	.....	.....	.....
12	.....	.....	2d course: 26th day, 7.5 to 60	2d course: 28th day	1st course: 4,800 to 3,350 2d course: 4,900 to 4,200 3d course: 5,200 to 3,800
13	1st course: 13th day	.....	.....	.....	.....
15	.....	.....	11.0 to 39.6	18th day	.....
18	2d course: diarrhea	1st course: 8th day	.....	.....	1st course: 13,200 to 2,750 2d course: 5,200 to 4,400
19	.....	.....	20.0 to 44.88	.....	.....
20	2d course: vomiting and diarrhea for 2 days	1st course: Fainted on 3d and 5th days	.....	.....	.....
22	.....	1st course: 4th day	21.8 to 102 (may not be due to drug)	.....	.....
23	.....	.....	21.4 to 40.12	.....	.....
25	1st course: nausea and vomiting 3d day; diarrhea for 15 days 2d course: nausea and vomiting 4 days (pyridoxine)	1st course: 18th day	.....	.....	1st course: 8,700 to 3,600
26	1st course: nausea 1st and 2d days; later vomiting during periods of obstruction	.....	.....	.....	.....
27	1st course: vomiting and hemoptysis for 9 days 2d course: for 5 days	.....	.....	.....	.....
28	.....	.....	.....	1st course: 6th and 25th days	.....

TABLE 4.—*Incidence of Toxic Manifestations in Thirty-Three of Forty-Two Patients Given Oral Treatment with Triethylene Melamine—Continued*

Case No.	Nausea, Vomiting, Diarrhea	Weakness	Temporary Increase in Urea Nitrogen Mg./100 Cc.	Transient Incidence of R.B.C. in Urine	Temporary Decrease in W.B.C./Cu. Mm. Below Normal Range
29	.....	1st course: 5th day 2d course: 13th day	1st course: 6th day 13.94 to 34.0	2d course: 11th, 19th, 26th, 32d, 49th days	1st course: 8,900 to 3,050 2d course: 6,700 to 3,200
30	.....	1st course: 15th day	1st course: 14.96 to 44.2 after 36 days 2d course: 17.68 to 43.52	.....	.....
31	.....	.....	.....	.....	5,050 to 3,250
32	2d course: diarrhea 10th day 5th course: diarrhea 3d day 6th course: nausea 3d day	1st course: 10th day 6th course: 9th day	.....	5th course: 16th day 6th course: 1st day 7th course: 18th day	5th course: 7,100 to 4,700
33	1st course: vomiting 2d day 2d course: vomiting 3d and 5th days	1st course: 3d day	.....	.....	2d course: 7,700 to 4,100
34	.....	1st course: 8th and 9th days	1st course: 10th day 10.88 to 15.3	.....	1st course: 8,450 to 3,750 2d course: 6,500 to 4,600
36	1st course: vomiting 1st day	.....	.....	.....	1st course: 7,750 to 4,700 2d course: 5,600 to 4,100 4th course: 7,800 to 3,850 5th course: 5,500 to 4,100
37	1st course: diarrhea 4th and 5th days	3d course: 2d and 3d days	.....	3d course: 12th, 31st, 58th, 164th, 171st, 173d days	1st course: 9,700 to 3,100 3d course: 8,100 to 3,950
38	2d course: nausea 1st to 3d days	.....	.....	.....	3d course: 16,000 to 4,000
39	1st course: nausea 2d day	1st course: 5th day 4th course: 2d day 5th course: 3d day 6th course: 5th day	.....	.....	6th course: 29,000 to 2,950
40	1st course: diarrhea 5th and 6th days 2d course: diarrhea 3d to 6th days	.....	.....	....	2d course: 6,050 to 2,300
41	1st course: vomiting 3d to 8th days; diarrhea 12th to 14th days	.....	.....	.....	1st course: 10,900 to 2,250 2d course: 5,000 to 3,150 3d course: 7,650 to 2,800 4th course: 6,250 to 2,900
42	1st course: nausea and vomiting 10th hr. to 6th day	.....	.....	4th course: 7th day 5th course: 48th day 6th course: 35th day 7th course: 5th, 69th, 77th day	2d course: 9,100 to 4,100 5th course: 7,600 to 3,950 6th course: 6,050 to 4,600

the drug occurred in patients who had shown these symptoms in previous courses. However, the prolonged course of treatment did not alleviate the delayed toxic effects. The therapeutic effectiveness seemed to be the same whether the course of 15 mg. was administered in three days or in fifteen days. In nine patients there were no toxic reactions during treatment. Table 4 summarizes the symptoms of toxicity observed in 33 of the 42 patients included in this study.

In two patients (Case 40 and 41) persistent leucopenia occurred after treatment with triethylene melamine. Administration of the citrovorum factor [5] was instituted in an attempt to increase the total white blood cell count. The patient for whose condition a diagnosis of lymphosarcoma was made (Case 41) had a white blood cell count which fluctuated between 2,900 and 3,100 for 16 days following triethylene melamine therapy. The citrovorum factor, 3 mg. intramuscularly daily, was administered, and the white blood cell count increased from 3,700 the first day of treatment to 4,700 in 12 days. When use of the citrovorum factor was discontinued, the white blood cell count again decreased progressively during the next 14 days to 2,800. Resumption of treatment with the citrovorum factor resulted in an increase of the total white blood cell count to 5,250 in five days. In the patient with Hodgkin's disease (Case 40), the white blood cell count had ranged from 2,300 to 2,800 for nine days following triethylene melamine therapy. When the citrovorum factor, 3 mg. intramuscularly daily, was given, the white blood cell count increased within seven days to 5,550. Whether, in these two cases, the white blood cell count would have returned to normal without use of the citrovorum factor, cannot be determined, and further studies along these lines should be undertaken.

CONCLUSION

We have treated 42 patients suffering from neoplastic diseases with triethylene melamine. Of this group, 18 showed improvement. The most dramatic improvement was noted in patients with lymphosarcoma, Hodgkin's disease, chronic myelogenous leukemia, and chronic lymphatic leukemia. Moderate improvement occurred in patients with fibrosarcoma, reticulum-cell sarcoma, and mycosis fungoides. No improvement was observed in any of the patients with carcinoma studied.

A close correlation was observed between the reaction of human tumors in tissue culture subjected to triethylene melamine and the tumors in the patients treated with triethylene melamine.

The citrovorum factor was used in two cases to correct the leucopenia which developed after treatment with triethylene melamine.

Further investigations with triethylene melamine in the treatment of sarcomas and related diseases should be conducted.

Miss Inga Hjelt and Miss Bernice Gitler gave technical assistance in this study.

5. "Leucovorin" used in this investigation was furnished through the courtesy of the Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

KLEBSIELLA PNEUMONIAE MENINGITIS

Review of the Literature and Report of a Case with Bacteremia and Pneumonia, with Recovery

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KLEBSIELLA pneumoniae (Friedländer's bacillus) meningitis is one of the less common forms of meningeal infection. Its rarity requires continued case analysis and reviews of the literature for its more accurate clinical description. The advent of the antibiotics and the increased possibility of cures suggest a reevaluation of therapeutic measures.

The bacillus was first identified by Friedländer in 1882, and the first case of meningitis due to this organism was reported by Weichselbaum in 1888. Thereafter, reports of K. pneumoniae meningitis were sporadic. In 1943 Ransmeier and Major [1] collected 30 cases from the literature. In 1949 Sadusk, and associates [2] assembled 54 instances of the infection; only 5 of the patients recovered. Bombardier's [3] extensive review in 1950 disclosed 72 cases of meningitis due to this organism. In this communication 118 cases of K. pneumoniae meningitis, including 31 with recovery, gathered from the world's literature to date are reviewed. One additional case of K. pneumoniae meningitis with recovery following aureomycin and streptomycin therapy is presented.

REPORT OF CASE

A 45-year-old Negro woman was admitted to the Homer G. Phillips Hospital, Feb. 17, 1951, complaining of occipital headache, fever, chills, and left lower lateral chest pain of four days' duration. There had been no recent upper respiratory infection. On the second day of this episode she experienced polyuria, increasing to the time of admission. The patient had been perfectly well prior to the onset of her present illness. She had noted no previous symptoms of diabetes. The family history disclosed a diabetic sister.

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1. Ransmeier, J. C., and Major, J. W.: Friedländer's Bacillus Septicemia and Meningitis: Report of a Case and Autopsy, with an Analysis of 29 Cases Collected from the Literature, Arch. Int. Med. **72**:319-328 (Sept.) 1943.

2. Sadusk, J. F.; Relman, A. S.; Wagner, R. R., and Barnett, R.: Friedländer's Bacillus Meningitis Treated with Streptomycin, Am. J. Med. **6**:522-529 (April) 1949.

3. Bombardier, J. P.: Friedländer's Bacillus Meningitis, Ann. méd. **51**:543-592, 1950

Physical examination revealed an obese, acutely ill, febrile, somewhat lethargic middle-aged woman, sweating profusely and complaining of left chest pain accentuated by deep inspiration. The temperature was 104 F., the pulse rate, 120 per minute, and the respiratory rate, 32 per minute. The blood pressure was 120/72. Funduscopic examination disclosed old waxy exudates in the left retina. Otherwise the eyes and the ears, nose and throat were normal. Fine moist rales were heard at the base of the left lung. The heart was not enlarged, and no murmurs were noted. The abdomen was not remarkable. Vaginal examination revealed a uterine myoma rising 7 cm. above the symphysis pubis. Rectal examinations disclosed no abnormality. No nuchal rigidity, Kernig, or Brudzinski signs were noted.

Examination of the blood indicated a red cell count of 5,200,000 per cubic millimeter, a hemoglobin concentration of 16 gm. per 100 cc. and leucocytes 7,700 per cubic millimeter, with 75% neutrophils (10% stabforms), 23% lymphocytes, and 2% monocytes. Urinalysis revealed no reaction for albumin, a 4+ Benedict reaction for sugar, a 3+ reaction for acetone (with sodium nitroprusside), and occasional granular casts on microscopic examination. The blood sugar was 307 mg. and the nonprotein nitrogen 19 mg. per 100 cc. The Kahn test gave a negative reaction. A roentgenogram of the chest presented soft, patchy infiltrations in both lung fields, more marked at the base of the right lung.

The patient was treated with insulin, dextrose in saline solution, and lactate solution, with remission of the acetonuria. She received 600,000 units of procaine penicillin in aluminum monostearate every eight hours. The following day, the temperature rose to 105 F. and she complained bitterly of occipital headache. Nuchal rigidity and Kernig and Brudzinski signs were present. Lumbar puncture yielded xanthochromic, turbid fluid which quickly formed a large gelatinous pellicle. The dynamic pressure of the spinal fluid was normal. A count after pellicle formation showed 1,800 cells; 95% were polymorphonuclear leucocytes, and 5% were lymphocytes. Chemical study of the spinal fluid disclosed a protein value of 570 mg. per 100 cc., 658 mg. of chlorides, and 198 mg. of sugar. The Wassermann reaction was negative.

No organisms were demonstrable in the Gram stain. The spinal fluid was inoculated directly into thioglycollate broth and on Sabouraud's dextrose-agar medium and Petragnani's medium (composed of potato, egg, glycerin, and malachite green). Two blood-agar plates were inoculated, one of which was incubated aerobically and the other under carbon dioxide. A blood culture was made with infusion broth. Penicillin (20,000 units) was instilled intrathecally.

The following morning, the third day, there was a luxuriant growth of colonies 0.3 to 0.5 cm. in diameter, grayish-white, glistening, convex, highly mucoid, and without hemolysis on blood-agar. A Gram stain of the organisms from the agar plates, the thioglycollate broth, and the blood culture showed Gram-negative bacilli approximately 4.5 μ in length by 0.5 μ in width. An India-ink preparation, which disclosed large capsules, was made from the blood-agar colonies.

On the third hospital day bacteriologic studies were not complete, although a Gram-negative rod had been identified. Administration of aureomycin, 3 gm. daily (orally), and of streptomycin, 2 gm. daily (intramuscularly) was, therefore, begun. Penicillin therapy was continued.

On the fourth hospital day the temperature had decreased to 101 F., but the patient remained acutely ill. There was persistent nuchal rigidity. At this time the offending organism was identified as K. pneumoniae on the basis of a quellung reaction with combined Type A and B antiserum. One cubic centimeter of a two-hour broth culture of the organism was injected into a mouse, and the mouse died after several hours. The organism recovered from the mouse also "quelled" with Type A and B K. pneumoniae antiserum. Tests showed the organism to be highly sensitive both to aureomycin and to streptomycin but not to penicillin. Quantitative sensitivities are not recorded because the technique employed was not properly standardized. Sugar fermentations, a positive reaction to the methyl red test, a negative Voges-Proskauer reaction, and the reduction of nitrates to nitrites also were suggestive of K. pneumoniae. However, it must be noted that these reactions of K. pneumoniae are variable and not definitive.[4] At this time streptomycin, 100 mg. administered intrathecally, was substituted for penicillin.

4. Breed, R. S.; Murray, E. G. D., and Hitchens, A. P.: Bergey's Manual of Determinative Bacteriology, Ed. 6, Baltimore, Williams & Wilkins Company, 1948, p. 458.

On the fifth day, the temperature had declined and the patient was more lucid, taking food by mouth for the first time. In view of the sensitivity of the organisms to streptomycin, aureomycin and penicillin administration was then discontinued.

On the sixth hospital day left chest pain recurred, associated with dyspnea. There were physical signs and roentgen evidence of frank left lower lobe consolidation without evidence of fluid. The patient coughed up a stringy, mucoid sputum from which K. pneumoniae was recovered.

On the eighth hospital day nystagmus and deafness in the right ear were evident. On the ninth day nuchal rigidity and headache had disappeared. The spinal fluid had shown no pellicle for two days. Intrathecal administration of streptomycin was discontinued. The chest symptoms abated. Deafness and nystagmus disappeared on the 15th day. The bloody spinal fluids noted in the chart were apparently of traumatic origin.

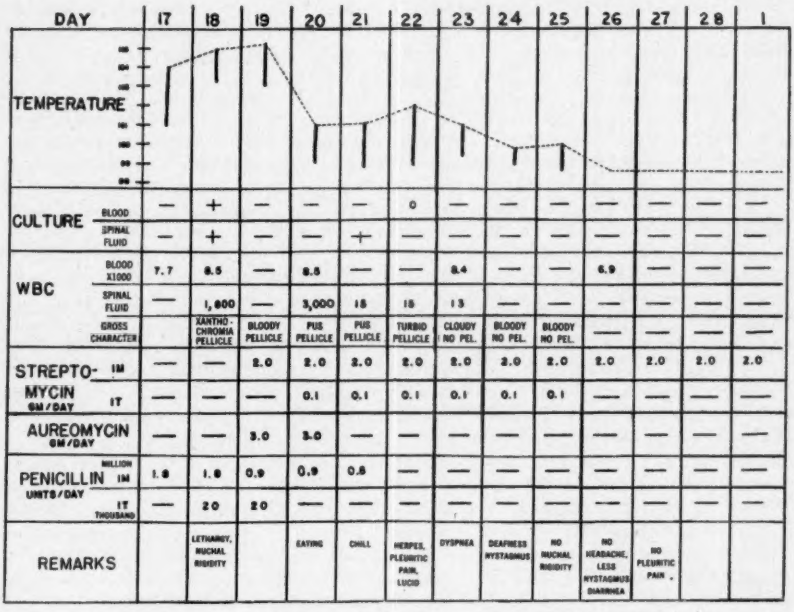

Chart showing clinical course of patient with K. pneumoniae meningitis.

The remainder of the clinical course was without event except for intermittent diarrhea controlled by symptomatic measures. Stool cultures were negative for K. pneumoniae. Intramuscular administration of streptomycin was discontinued on the 21st day, the patient having been afebrile for 10 days. Upper and lower gastrointestinal series and a cholecystogram were normal. An otorhinolaryngologic evaluation, including roentgenograms of the sinuses, was not remarkable. A roentgenogram of the chest was normal on the 27th hospital day.

The insulin requirement gradually diminished, so that on the 24th hospital day use of insulin was discontinued. No further glycosuria occurred, and the diabetes was controlled by diet alone. On the 30th hospital day the results of a dextrose-tolerance test confirmed the diagnosis of diabetes mellitus.

A lumbar puncture on the 33d hospital day revealed a clear fluid containing 15 lymphocytes, with normal dynamic pressure and sugar and protein levels. There was no growth on culture. The patient was discharged on the 34th hospital day on a diabetic diet without insulin.

COMMENT

In Table 1 there appear in chronological order 119 cases of K. pneumoniae meningitis gathered from previous reviews and additional scattered case reports.[5]

5. (*a*) Baehr, G.; Shwartzman, G., and Greenspan, E. B.: Bacillus Friedländer Infections, Ann. Int. Med. **10**:1788-1801 (June) 1937. (*b*) Committee on Chemotherapeutics and Other Agents, National Research Council: Streptomycin in the Treatment of Infections, J. A. M. A. **132**:70-77 (Sept. 14) 1946. (*c*) Trevett, G. I.; Nelson, R. A., and Long, P. H.: Clinical Use of Sulfadiazine in Therapy of Bacterial Infections Other Than Pneumonia, Bull. Johns Hopkins Hosp. **69**:303-313 (Oct.) 1941. (*d*) Burman, H. J.; Rosenbluth, M., and Burman, D.: Otorhinogenic Meningitis: A Report of 58 Cases, Arch. Otolaryng. **35**:687-719 (May) 1942. (*e*) Sheridan, P. E.: Liver Abscess, Pneumonia, and Empyema Due to Friedländer's Bacillus in Diabetes Mellitus: A Report of Two Cases with Recovery in One, New England J. Med. **233**:528-529 (Nov. 1) 1945. (*f*) Schloss, E. M.; Davidson, J. H., and Hilton, K. C.: Klebsiella Meningitis: A Case Cured with Streptomycin, Ann. Int. Med. **29**:540-545 (Sept.) 1948. (*g*) King, S.: Friedländer's Bacillus Meningitis, with Report of a Case Treated Unsuccessfully with Sulfadiazine, ibid. **24**:272-277 (Feb.) 1946. (*h*) Gilbert-Dreyfus; Zarachovitch, M.; Herrault, A., and Labignette: Postabortal Meningitis Due to Friedländer's Pneumobacillus: Rapid Recovery of a Patient in Preagonal Condition Due to Associated Penicillin and Sulfonamide Therapy, Bull. mém. Soc. méd. hôp. Paris **62**:511-513, 1946. (*i*) Gilbert-Dreyfus; Zarachovitch, M., and Herrault, A.: Septicemia Due to Friedländer's Pneumobacillus Cured with Mixed Penicillin and Sulfonamide Therapy, ibid. **62**:513-514, 1946. (*j*) Tartakoff, S.; Grynbaum, B., and Le Compte, P. M.: Friedländer's Bacillus Meningitis Treated with Streptomycin, New England J. Med. **235**:681-683 (Nov. 7) 1946. (*k*) Benhamou, E.; Destaing, F.; Leonardon, H., and Vargues, R.: Friedländer's Bacillus Meningitis: Case, Algérie méd., pp. 538-540 (Nov.-Dec.) 1946. (*l*) Gareiso, A.; Sagreras, P. O., and Vazquez, H. J.: Meningitis Due to Friedländer's Pneumobacillus in Childhood, Arch. argent. pediat. **28**:73-102 (Aug.) 1947. (*m*) Pulaski, E. J., and Matthews, C. S.: Streptomycin in Surgical Infections: III. Otitis Externa, Otitis Media, Mastoiditis, Brain Abscess, and Meningitis, Arch. Otolaryng. **45**:503-515 (May) 1947. (*n*) Hough, P. T., and Adelson, L.: Meningitis Caused by Friedländer's Bacillus or Aerobacter Aerogenes: Report of 2 Cases with Autopsies, Am. J. Clin. Path. **17**:534-537 (July) 1947. (*o*) Solomon, S.: Wound Infections with Friedländer Bacillus Followed by Meningitis, New England J. Med. **237**:149-152 (July 31) 1947. (*p*) Paine, T. F.; Murray, R.; Sealer, A. O., and Finland, M.: Streptomycin in the Treatment of Meningitis: Report of 27 Cases Treated at the Boston City Hospital, Ann. Int. Med. **27**:494-518 (Oct.) 1947. (*q*) Thurel, R., and Durupt, L.: Meningitis Due to Friedländer's Bacillus Cured by Penicillin, Rev. neurol. **79**:258-259 (April) 1947. (*r*) Tolentino, P.: Meningitis Caused by Polymorphous Bacteria of the Mucosus Group: A Case in a Newborn, Riv. Ist. sieroterap. ital. (sez. I) **22**:189-201 (July-Sept.) 1947. (*s*) Ghiselin, A. D., and Robertson, R. B.: Friedlaender's Bacillus Meningitis Secondary to Otitis Media, Arch. Otolaryng. **45**:432-445 (April) 1947. (*t*) Jacob, S. S., and Top, F. H.: Friedländer's Bacillus Meningitis: Report of 7 Cases with 2 Recoveries, Ann. Int. Med. **28**:1003-1009 (May) 1948. (*u*) Hyde, B., and Hyde, L.: Friedländer's Bacillus Meningitis, California Med. **69**:229-230 (Sept.) 1948. (*v*) Mechali, R.: Association of Penicillin and Sulfonamides in Therapy of Meningitis Caused by Friedländer's Bacillus, Algérie méd., pp. 355-357, June-July, 1948. (*w*) Fisher, G. J.: Friedländer's Bacillus Meningitis, Treated in Part with Streptomycin with Recovery, New York J. Med. **48**:202-204 (Jan.) 1948. Jobin, J. B., and Lessard, R.: (*x*) Meningitis Caused by Friedlander's Pneumobacillus: A Case with Recovery, Laval méd. **13**:973-976 (Oct.) 1948; (*y*) Meningitis Caused by Friedländer's Pneumobacillus: A Case with Recovery, Union méd. Canada **77**:1485 (Dec.) 1948. (*z*) Ayvazian, L. F.: Friedländer's Bacillus Meningitis Successfully Treated with Streptomycin: Consideration of Friedländer's Bacillus Infections in Diabetes, Am. J. Med. **5**:470-477 (Sept.) 1948. (*a'*) Daniel, W. A.: B. Mucosus Capsulatus (Friedländer's) Meningitis: Recovery of a 3 Week-Old Infant Treated with Sulfadiazine and Streptomycin, Pediatrics **3**:3-8 (Jan.) 1949. (*b'*) Conn, J. J., and Rosenow, O. F.: Mixed Meningitis: A Case of Combined Pneumococcus and Klebsiella

These include 89 more cases [5c-e'] than were assembled in the last complete review in English, that of Ransmeier and Major.[1] In a number of instances the detailed bacteriologic criteria for diagnosis were not recorded, but because of their inclusion in previous reviews these cases are listed here. In the 63 cases in which results of direct smears were recorded, 54 were positive and 9 were negative for K. pneumoniae. Of 59 cases in which results of spinal fluid cultures were recorded, 57 were positive and 2 were negative for K. pneumoniae. In only one case, that of Debré,[6] were both smear and culture negative. However, in this instance, the blood culture was positive for K. pneumoniae.

The cases of Mackay and Lapointe [7] and of Benhamou and Destaing [6] are excluded from Table 1 because of negative spinal fluid smears and cultures, with otherwise inconclusive evidence of K. pneumoniae infection of the meninges. The second case of Malis [5d'] with mastoiditis and K. pneumoniae bacteremia was not included because it was more probably meningismus than true meningitis. The cases of Neil and Blechman [8] and of Debakey and Pulaski,[9] though they have been included in previous reviews, are likewise excluded as rather due to Aerobacter aerogenes. However, it must be noted that in the avirulent, acapsular-phase K. pneumoniae, A. aerogenes, and colon bacilli are indistinguishable.[10]

Eleven additional cases have been noted in reviews of 6,051 cases of meningitis of varied causation.[11] These cases are not included. Yet they demonstrate well the infrequency of this disease.

Table 2 illustrates the distribution of the primary focus of infection in the cases reported. The high incidence of otorhinolaryngologic and "undetermined" foci is to be noted. Similarly, Ransmeier and Major [1] found foci in the ear, nose, and throat more frequently in adults and an "undetermined" focus more frequently in children under 3 years of age. The respiratory tract was less commonly the focus of infection according to the statistics of Baehr.[5a] He implicated the respiratory tract in only 12% of all K. pneumoniae infections and found the gastrointestinal

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Meningitis with Recovery, Arch. Int. Med. **85**:924-932 (June) 1950. (*c'*) Di Figlia, S. E., and Cramer, C.: Friedländer's Bacillus Meningitis with Liver Abscess and Recurrent Bacteremia and Analysis of Cases Receiving Specific Therapy, New York J. Med. **51**:761-765 (March) 1951. (*d'*) Malis, S.: Pneumobacillus (Friedländer's) Meningitis Secondary to Otitis Media: Report of 2 Cases, Arch. Otolaryng. **12**:162-174 (Aug.) 1930. (*e'*) Rothschild, K.: Meningitis Caused by Friedländer's Bacillus: A Case with Recovery, J. A. M. A. **97**:1956-1959 (Dec. 26) 1931. (*f'*) Robertson, C. S.: Meningitis Due to B. Friedländeri: Recovery of a Case Treated with Sulfapyridine, Canad. M. A. J. **45**:70-71 (July) 1941; cited by Ransmeier and Major.[1]

6. Cited by Bombardier.[8]

7. Mackay, A., and Lapointe, R.: Acute Meningitis (One Case), Union méd. Canada **79**:578-581 (May) 1950.

8. Neil, C. L., and Blechman, H. F.: Aerobacter Aerogenes Meningitis, Bull. U. S. Army M. Dept. **7**:722-726 (Aug.) 1947.

9. Debakey, M., and Pulaski, E. J.: An Analysis of the Experience with Streptomycin Therapy in U. S. Army Hospitals, Surgery **20**:749-760 (Dec.) 1946.

10. Osterman, E., and Rettger, L. F.: A Comparative Study of Organisms of the Friedländer and Coli-Aerogenes Groups (Pathogenicity, Biochemical Reactions and Serologic Relationships), J. Bact. **42**:721-743 (Dec.) 1941.

11. Jacob and Top.[5t] Yaskin, J. C.: Differential Diagnosis of Bacterial Meningitis of Aural and of Nasal Origin, Arch. Otolaryng. **27**:444-451 (April) 1938.

TABLE I.—*Data on 119 Cases of K. Pneumoniae Meningitis*

Author	Date	Sex	Age	Probable Primary Focus	Other Extra-meningeal Foci	Blood Culture	Spinal Fluid Culture	Direct Smear	Other Disease	Therapy	Outcome
Weichselbaum *	1888	F	55 yr.	Otitis media	Paranasal sinusitis; mastoiditis	.....	.....	Pos.	Glycosuria	.....	Death
Dmochowski *	1894	M	54 yr.	Sphenoid and maxillary sinusitis	Osteomyelitis of face; brain abscess	.....	.....	.....	.....	.....	Death
Etienne †	1895	M	33 yr.	Pneumonia	Empyema; arthritis	.....	.....	.....	.....	.....	Death
Brunner *	1896	M	55 yr.	Otitis	Petrositis; sinus thrombosis; renal embolic abscesses	.....	.....	Pos.	Hepatic cirrhosis	.....	Death
Scheib, cited by Bombardier,[3] Gareiso & others,[61] Pulaski & Matthews [5m]	1899	..	8 days	Otitis	.....	.....	Pos.	Pos.	Prematurity	.....	Death
Jassniger †	1901	M	16 yr.	Sphenoid sinusitis	Cavernous sinus phlebitis	.....	.....	.....	.....	.....	Death
Beitzke ‡	1904	..	17 days	Undetermined	.....	.....	.....	Pos.	Congenital syphilis; icterus; atelectasis; nephritis	.....	Death
Lequeux §	1906	..	4 days	Umbilical infection	.....	Pos.	Pos.	Pos.	.....	.....	Death
Guinon & Simon §	1910	..	5 yr.	Otitis media	.....	.....	Neg.	Pos.	.....	.....	Recovery; incoordination of gait
Sireday, Lemaire, & de Jong †	1912	M	26 yr.	Pharyngitis	.....	.....	.....	.....	Splenomegaly; icterus	.....	Death
Bonhoff & Esch *	1912	..	Newborn	Otitis	.....	.....	.....	Pos.	.....	.....	Death; intracranial hemorrhage
Elias,‖ Case 2	1912	..	17 days	Umbilical infection	.....	.....	.....	Pos.	Terminal pneumonia	.....	Death
Zange ¶	1912	M	61 yr.	Otitis; mastoiditis	Abscess of jugular bulb	.....	Pos.	Pos.	.....	Mastoidectomy	Death
	1912	M	28 yr.	Otitis media	.....	.....	Pos.	Pos.	.....	Mastoidectomy	Death
Neal ‡	(1915) 1926	M	2½ yr.	Otitis; mastoiditis	Pneumonia	Pos.	Pos.	Neg.	.....	Mastoidectomy	Recovery
Rénon & Blamoutier *	(1920) 1921	F	44 yr.	Otitis	Petrositis	.....	.....	Pos.	Glycosuria	No surgery	Death
Broca, Ranque, & Sanez §	(1920)	..	2 mo.	Undetermined	.....	.....	.....	Pos.	.....	.....	Death
Neal ‡	1920	M	45 yr.	Otitis	.....	Pos.	.....	.....	Diabetes mellitus; nephritis	.....	Death
Debré, Semelaigne, & Lelong §	1924	..	21 days	Undetermined	.....	.....	.....	Pos.	Bronchopneumonia	.....	Death; hydrocephalus
Elias,‡ Case 1	1924	M	62 days	Bronchitis	Paravertebral pneumonia	Neg.	.....	.....	.....	.....	Death
Menetrier & Bertrand-Fontaine †	1924	M	33 yr.	Undetermined	.....	.....	.....	.....	Glycosuria	.....	Death
Lion & Minvielle †	1924	M	38 yr.	Pneumonia	Lung abscess	.....	.....	.....	.....	.....	Death
Dufourt, Delattre, & Bonnet ‡	(1925) 1926	..	9 mo.	Arthritis of ankle and elbow	.....	Pos.	.....	.....	.....	.....	Death
Debré, Broca, & Birós §	....	..	6 days	Undetermined	.....	Pos.	Pos.	Pos.	Cephalhematoma	.....	Recovery; impaired vision
Legrand ‡	1925	F	23 yr.	Undetermined	.....	.....	.....	.....	Central nervous system syphilis	.....	Death

Papandrea,‡ Case 1	1927	F	5 mo.	Pneumonia	Pleuritis; pericarditis	.....	.....	Pos.	Congenital syphilis	.....	Death
Jacob & Top,[51] cited by Bombardier,[3] Case 6	(1927) 1948	F	53 yr.	Mastoiditis	.....	Pos.	Pos.	.....	.....	.....	Death
Papandrea,§ Case 2	1927	M	2½ yr.	Umbilical infection	.....	Pos.	Pos.	Pos.	.....	.....	Death; hemorrhagic spinal fluid
Leenhardt, Boucomont, & Balmès §...	(1927) 1937	..	18 mo.	Undetermined	.....	.....	.....	Pos.	Cephalhematoma	.....	Death
Brain & Valentine *	1928	M	22 yr.	Otitis; mastoiditis	.....	Pos.	.....	.....	.....	.....	Death
Deane & Shera †	1928	F	71 yr.	Cholecystitis	.....	.....	.....	.....	.....	.....	Death
Hesse ¶	1929	M	15 yr.	Otitis	.....	.....	Pos.	Pos.	.....	.....	Death
Cascelli ‡	1930	F	42 yr.	.....	.....	.....	.....	.....	.....	.....	Death
Jacob & Top,[51] cited by Bombardier,[3] Case 1	(1930) 1948	M	47 yr.	Lobular pneumonia	.....	Neg.	Pos.	.....	.....	.....	Death
Mallis,[54] cited by Bombardier,[3] Gareiso & others,[51] Ghiselin & Robertson [58]	1930	M	5 yr.	Otitis media	Labyrinthitis	Pos.	Pos.	Pos.	.....	Mastoidectomy	Death
Ruelle §	(1931) 1932	..	4 mo.	Undetermined	.....	.....	.....	Pos.	Prematurity	.....	Death
Rothschild,[56] cited by Ransmeier & Major,[1] Bombardier,[3] Ghiselin & Robertson [58]	1931	M	34 yr.	Otitis	Mastoiditis; subdural abscess	Neg.	Pos.	Pos.	Glycosuria	Mastoidectomy	Recovery
Comte, Lévy-Bruhl, & Dany **	1931	M	50 yr.	Undetermined	.....	Pos.	.....	.....	.....	.....	Death
Le Sourd & Draillard ‡	1932	F	42 yr.	Undetermined	Liver abscess	.....	.....	.....	Cranial trauma	.....	Death
Schiavone & Idelsohn §	(1932) 1934	..	4 yr.	Rhinitis	.....	.....	.....	Pos.	Surgical treatment for temporal sebaceous cyst	.....	Death
Babonneix & Rion §	1933	..	21 days	Undetermined	.....	.....	.....	Pos.	Hydrocephalus	.....	Death
Jacob & Top,[51] cited by Bombardier,[3] Case 2	(1933) 1948	M	49 yr.	Otitis media	Brain abscess; osteochondritis of rib	Pos.	Pos.	.....	.....	.....	Death
Fothergill & Sweet †	1933	M	4 wk:	Undetermined	.....	Pos.	.....	.....	Enteritis	.....	Death
Gowen †	1934	F	63 yr.	Otitis	Mastoiditis; abscess of neck and arm	.....	.....	.....	.....	.....	Death
Railliet & Grinsbourg §	1934	..	11 yr.	Undetermined	Bronchopneumonia	Pos.	.....	Pos.	Bronchopneumonia	.....	Death; petechial epistaxis
Railliet, Perono, & Morel ‡	(1935) 1936	M	19 yr.	Undetermined	.....	Pos.	.....	.....	.....	.....	Death
Davis & Fernando,** Case 1	1935	F	29 yr.	Uterine infection	.....	.....	.....	.....	Abortion	.....	Death
Case 2	1935	M	1 mo.	Undetermined	Basal pneumonia	.....	.....	.....	.....	.....	Death
Rimoldi & Montagna ‖	1935	..	3 days	Undetermined	.....	.....	Pos.	Pos.	.....	.....	Death
Hyde & Hyde [52]	(1935) 1948	M	37 yr.	Pneumonia	.....	Pos.	Pos.	.....	.....	.....	Death
	1948	M	52 yr.	Pneumonia	.....	Pos.	Pos.	.....	.....	.....	Death
Von Moritz ‖	1936	..	4 mo.	Undetermined	.....	.....	Pos.	Pos.	Pulmonary tuberculosis	.....	Death
Leenhardt, Boucomont, & Balmès ‡...	1937	..	4½ mo.	Bronchitis	.....	Neg.	Pos.	Pos.	Gastroenteritis; bronchitis	.....	Death
Baehr & others,[55] cited by Breed & others [4]	1937	..	.....	Mastoiditis	.....	Pos.	Pos.	Pos.	.....	Mastoidectomy	Death
Sicard & Pluvinage †	1937	F	58 yr.	Frontal sinusitis	Osteomyelitis of frontal bone	Pos.	.....	.....	.....	.....	Death

TABLE 1.—*Data on 119 Cases of K. Pneumoniae Meningitis—Continued*

Author	Date	Sex	Age	Probable Primary Focus	Other Extra-meningeal Foci	Blood Culture	Spinal Fluid Culture	Direct Smear	Other Disease	Therapy	Outcome
Jacob & Top,[51] cited by Bombardier,[3] Case 3	(1937) 1948	F	39 yr.	Otitis	.....	.....	Pos.	Pos.	Diabetes mellitus	.....	Death
Mippi ‖	1938	..	8 mo.	Undetermined	.....	.....	.....	Pos.	.....	.....	Death
Nobécourt ‡	1938	M	8½ mo.	Undetermined	.....	.....	.....	.....	Prematurity	.....	Death
Lombard & Montzain ‡	1938	M	7 yr.	.....	.....	.....	Pos.	.....	Cranial trauma; fracture of tibia	Sulfonamides	Recovery; no residua
Garcia & Aballes ‡	(1939) 1940	M	2 yr.	Undetermined	.....	.....	Pos.	.....	.....	Sulfapyridine; autovaccine	Recovery
Kolmer & Rule †	1939	M	36 yr.	Frontal, ethmoid, and sphenoid sinusitis	.....	Neg.	.....	.....	.....	Sulfapyridine	Death
Slobozianu & Ionescu †	1940	F	Newborn	Pneumonia	.....	.....	.....	.....	.....	.....	Death; intracranial hemorrhage
Montes & Real **	1940	M	2 yr.	Undetermined	.....	.....	.....	.....	.....	Sulfapyridine	Recovery
Sheridan,[5c] cited by Bombardier [3]	1940	M	65 yr.	Undetermined	Lung, liver, and kidney abscesses	Pos.	Pos.; Type A	.....	Diabetes mellitus	Sulfapyridine; anti-K. pneumoniae serum	Death
Robertson **	1941	M	49 yr.	Maxillary sinusitis	Bronchopneumonia	Neg.	.....	.....	Diabetes mellitus	Sulfapyridine; autovaccine	Recovery
Gareiso & others,[51] Case 1	(1941) 1947	M	22 mo.	Undetermined	.....	.....	Pos.	Pos.	Coryza; debility	Sulfonamide	Death
Cautorne ‡	1941	M	9 yr.	Bronchitis	.....	.....	.....	Pos.	.....	Sulfonamide	Cure; no residua
Hodes, cited by Trevett & others [6c]	1941	..	.....	.....	.....	.....	.....	.....	.....	Sulfadiazine	Cure
Ransmeier & Major [1]	(1942) 1943	M	73 yr.	Undetermined	Miliary visceral abscess	Pos.	Pos.; Type B	Neg.	Diabetes; bronchitis; enteritis	Sulfapyridine	Death
Thomas, Perlés, Planques, & Fournial ‡	1942	M	Adult	.....	.....	.....	.....	.....	.....	.....	Death
Mackay & Morris ‡	1942	M	56 yr.	Prostatic abscess	.....	.....	.....	.....	.....	Sulfathiazole	Death
Burman & others [5d]	1942	..	.....	Mastoiditis	.....	.....	Pos.; Type A	.....	.....	Mastoidectomy; sulfapyridine	Recovery
Gareiso & others,[51] Case 2	(1943) 1947	F	7 mo.	Undetermined	.....	.....	Pos.	Pos.	Influenza	Sulfonamide	Death
Mori, cited by Sadusk & others,[3] Gareiso & others [51]	1943	..	20 mo.	Pharyngitis	.....	.....	Pos.	Pos.	.....	Sulfadiazine	Recovery; no residua
Gareiso & others,[51] Case 3	(1944) 1947	M	6 mo.	Undetermined	.....	.....	Pos.	Pos.	Cephalhematoma	Sulfonamide	Death
Jacob & Top [51]	(1944) 1948	F	56 yr.	Mastoiditis	.....	Neg.	Pos.; Type A	Pos.	Diabetes mellitus	Mastoidectomy; sulfadiazine & sulfathiazole; penicillin IM & IT ††	Recovery
Solomon [5c]	(1944) 1947	M	26 yr.	Wound infection	.....	Pos.	Pos.	Pos.	Fracture of ilium	Sulfadiazine; penicillin IM & IT	Death
	(1944) 1947	M	19 yr.	Fracture of skull; craniotomy	Pneumonia; brain abscess	.....	Pos.	Pos.	.....	Sulfadiazine; penicillin IM & IT	Death
	(1944) 1947	M	29 yr.	Laceration of cauda equina	.....	.....	.....	.....	Perforation of intestine; pulmonary infarction	Sulfonamides; penicillin	Death
Sobel, Bardier, Bovisson, & Escat ‡	(1944) 1947	M	26 yr.	War wound of hip	.....	.....	Pos.; Type A	.....	.....	Sulfonamides; penicillin	Death

Ghiselin & Robertson [58]	1945	M	48 yr.	Otitis; mastoiditis	Abscess of sigmoid sinus	.....	Pos.; Type A	Neg.	Diabetes mellitus	Mastoidectomy; sulfadiazine; penicillin IM & IV	Recovery
Gareiso & others,[51] Case 4	(1945) 1947	F	2 mo.	Undetermined	.....	.....	Pos.	Pos.	.....	Sulfonamide	Death
Case 5	(1945) 1947	F	18 days	Undetermined	.....	.....	Pos.	Pos.	.....	Sulfonamide	Death
Case 6	(1945) 1947	F	5 yr.	Undetermined	.....	Neg.	Pos.	Pos.	.....	Sulfamerazine; penicillin IM & IT	Recovery; mutism; disturbance of gait
Case 7	(1945) 1947	F	2 yr.	Undetermined	.....	.....	.....	Pos.	.....	Sulfonamide; penicillin IM & IT	Recovery; hydrocephaly; paraplegia; mental retardation
Hough & Adelson,[5n] cited by Bombardier [3]	(1945) 1947	M	1 mo.	Urinary tract infection	.....	Pos.	Pos.	.....	Congenital valve of urethra	Sulfadiazine; streptomycin IM & IT	Death
Fisher [5w]	1945	F	65 yr.	Otitis media	.....	Neg.	Pos.; Type A	Pos.	.....	Sulfadiazine; penicillin IM & IT; streptomycin IM & IT	Recovery
Bernard & Thomas [7]	1945	M	48 yr.	Otitis; labyrinthitis	.....	.....	.....	.....	.....	Sulfonamides	Recovery
Tartakoff & others [5j]	(1945) 1946	M	49 yr.	Craniotomy wound	Positive throat culture for K. pneumoniae	Pos.; Type B	Pos.; Type B	.....	Meningioma	Sulfadiazine; penicillin IM & IT; streptomycin IV & intracisternally	Death; apparent recovery, then death from pulmonary embolism
Schloss & others [5f]	1945	M	21 yr.	Mastoiditis; ethmoiditis	.....	.....	Pos.	Pos.	.....	Sulfadiazine; penicillin IM & IT; streptomycin IM & IT	Recovery
Gareiso & others,[51] Case 8	(1946) 1947	M	2 yr.	Pharyngitis	.....	.. ..	Pos.	Pos.	.....	Penicillin IM & IT	Death
Case 9	(1946) 1947	M	4 yr.	Undetermined	.....	.....	Pos.	Pos.	Coryza	Sulfamerazine; Penicillin IM & IT	Recovery; no sequelae
Sadusk & others [3]	(1946) 1949	F	60 yr.	Cholecystitis; cholelithiasis	Liver abscess	Pos.; Type B	Pos.; Type B	Pos.	Syphilitic heart disease	Sulfadiazine IV; streptomycin IM & IT	Improvement, then death from cardiac failure
King,[5s] cited by Bombardier [3]	(1946) 1947	..	6 mo.	Enteritis	.....	Pos.	.....	.....	Bronchopneumonia	Sulfadiazine	Death
Hough & Adelson,[5n] cited by Bombardier [3]	(1946) 1947	F	29 yr.	Suppurative endometritis	Renal abscess	Pos.	Pos.	.....	.....	Sulfonamide; penicillin IM & IT; streptomycin IT	Death
Benhamou & others [5k]	1946	M	35 yr.	Undetermined	.....	Pos.	Pos.	Neg.	Hemorrhagic diathesis; hepatosplenomegaly	Sulfonamide	Death
Gilbert-Dreyfus & others [51]	1946	F	22 yr.	Suppurative endometritis	.....	Neg.	Pos.	Pos.	.....	Sulfadiazine; penicillin IM & IT	Recovery
Gilbert-Dreyfus & others [5h]	1946	M	17 yr.	Undetermined	.....	Pos.	.....	.....	Diarrhea	Sulfadiazine; penicillin IM & IT	Recovery

TABLE 1.—*Data on 119 Cases of K. Pneumoniae Meningitis—Continued*

Author	Date	Sex	Age	Probable Primary Focus	Other Extra-meningeal Foci	Blood Culture	Spinal Fluid Culture	Direct Smear	Other Disease	Therapy	Outcome
Pulaski & Matthews [8m]	1946	M	21 yr.	Mastoiditis	Brain abscess	.....	.....	Pos.	.....	Mastoidectomy; sulfadiazine; penicillin; streptomycin IM & IT	Recovery
Ayvazian [8s]	(1946) 1948	F	48 yr.	Middle ear infection	.....	.....	Pos.	Neg.	Diabetes mellitus	Mastoidectomy; sulfadiazine; penicillin IM & IT; streptomycin IM & IT	Recovery
Jacob & Top,[8t] cited by Bombardier,[3] Case 5	(1946) 1948	M	55 yr.	Otitis media	Brain abscess; tracheal bronchitis; bronchopneumonia; mastoiditis	Neg.	Pos.; Type A	.....	.....	Sulfadiazine; penicillin IM & IT; streptomycin IM & IT	Death; left hemiplegia
Case 6	(1946) 1948	M	50 yr.	Mastoiditis	.....	Neg.	Pos.; Type A	Neg.	.....	Sulfadiazine; penicillin IM	Recovery
National Research Council,[8b] 2 cases...	1946	..	.....	.....	.....	.....	.....	.....	.....	Sulfadiazine; streptomycin IM & IT	Death
Paine & others [8p]	1947	F	70 yr.	Otitis media	.....	Pos.	Pos.	.....	.....	Sulfadiazine; penicillin IM & IT; streptomycin IM & IT	Death
Thurel & Durupt,[8q]	1947	F	25 yr.	Laminectomy; wound infection	.....	.....	Pos.	Pos.	Herniated intervertebral disk	Sulfonamide; penicillin IM & IT	Recovery
Debré,‡ Case 1	(1947) 1949	M	8 mo.	Mastoiditis	.....	.....	.....	.....	Enteritis	Penicillin; streptomycin	Death; hydrocephaly
Case 2	(1947) 1949	M	1 yr.	Otitis	.....	.....	.....	.....	.....	Paracentesis; sulfonamide; penicillin; streptomycin	Death
Case 3	(1947) 1949	M	10 days	.....	.....	.....	.....	.....	Bronchitis	Penicillin; streptomycin	Death
Case 4	(1947) 1949	M	1 mo.	Otitis	.....	.....	.....	.....	Bronchitis; subcutaneous abscess	Paracentesis; penicillin; streptomycin	Death
Case 5	(1947) 1949	M	1 yr.	Otitis; mastoiditis	Pyuria (K. pneumoniae)	.....	.....	.....	Bronchitis	Mastoidectomy; sulfonamide; penicillin; streptomycin	Death; hydrocephaly
Case 6	(1947) 1949	M	4 mo.	.....	.....	Pos.	Neg.	Neg.	Gastroenteritis	Sulfonamide; penicillin; streptomycin	Recovery
Tolentino [8r]	1947	F	3 days	Undetermined	.....	.....	Pos.	Pos.	Icterus; birth-trauma; pneumonia	Sulfapyridine; penicillin IV & in ventricles	Death

Mechall [5v]	(1947) 1948	M	15 mo.	Undetermined	.....	.....	.....	Pos.	.....	Sulfonamide; penicillin IM & IT	Death
Daniel,[5a'] cited by Bombardier [3]	(1948) 1949	M	3 wk.	Undetermined	.....	.....	Pos.	Pos.	Diarrhea	Sulfadiazine; streptomycin IM & IT	Recovery
Jobin & Lessard,[5x, y] cited by Bombardier [3]	1948	F	27 yr.	Otitis	.....	.....	Pos.	Pos.	.....	Sulfadiazine; penicillin; streptomycin IM & IT	Recovery
Martin & Sureau [‡]	1950	F	12 yr.	Wound infection of head	.....	.....	.....	.....	.....	Sulfonamides; penicillin; streptomycin; chloramphenicol	Recovery
Conn & Rosenow [5b']	1950	M	60 yr.	Undetermined	.....	.....	Pos.; K. pneumoniae & pneumococci	Neg.; pneumococci only	Lobar pneumonia; pneumococcal meningitis	Sulfadiazine; penicillin IM & IT; streptomycin IM & IT	Recovery; deafness; partial blindness; disturbance of gait
Di Figlia & Cramer [5c']	1951	F	55 yr.	Enteritis	Liver abscess	Pos.	Pos.	.....	Diabetes mellitus; lower nephron syndrome	Sulfadiazine; streptomycin IM, IV, & IT	Death
Thompson & others	1951	F	45 yr.	Pneumonia	.....	Pos.	Pos.	Neg.	Diabetes mellitus	Penicillin IM & IT; streptomycin IM & IT; aureomycin	Recovery

* Cited by Ransmeier and Major,[1] Bombardier,[3] Ghiselin and Robertson.[5c]
† Cited by Ransmeier and Major,[1] Bombardier.[3]
‡ Cited by Ransmeier and Major,[1] Bombardier,[3] Gareiso and others.[5l]
§ Cited by Bombardier,[3] Gareiso and others.[5l]
‖ Cited by Gareiso and others.[5l]
¶ Cited by Ghiselin and Robertson.[5c]
# Cited by Bombardier.[3]
** Cited by Ransmeier and Major.[1]
†† IM means intramuscularly; IT, intrathecally, and IV, intravenously.

and hepatobiliary systems the most frequent sites of involvement. Wound infections of the umbilicus and especially of the meninges are seen to be frequent primary sites of this infection.

The incidence of diabetes complicating K. pneumoniae meningitis is significantly higher than in random population groups. Ten cases are reported with true diabetes mellitus and four with glycosuria of uncertain cause. The association of K. pneumoniae infections with diabetes mellitus is of some interest. In this connection Hoogerheide found increased virulence and greater capsule formation with a glucose concentration of 300 mg. per 100 cc. in the medium.[12]

The last examination of our patient, in June, 1951, revealed persistent elevation of the fasting blood sugar level and transitory glycosuria requiring small doses of protamine zinc insulin (10 to 15 units daily) for control. On these occasions there was no evidence of infection. This is, therefore, assumed to be a true case of diabetes mellitus, rather than one of glycosuria and ketosis complicating meningeal infection.

TABLE 2.—*Distribution of Foci in All Reported Cases of K. Pneumoniae Meningitis*

Focus	Total Cases	Recoveries	Deaths	Percentage Recoveries
Eye, ear, nose, throat	45	16	29	35.5
Lower respiratory tract	10	1	9	10.0
Gastrointestinal tract	4*	0	4	0.0
Genitourinary tract	2	0	2	0.0
Uterus	3	1	2	33.0
Arthritis	1	0	1	0.0
Wound infection	10	2	8	20.0
Undetermined†	44	12	32	27.2
	119			

* Two cases of cholecystitis.
† Includes cases in which the focus was not listed, as well as those in which it was undetermined.

Debilitating states of wide variety seem to be associated with and to predispose to K. pneumoniae meningitis.

The clinical features of K. pneumoniae meningitis are indistinguishable from those of other types of purulent meningitis. It is of interest that petechiae may occur.[5k,b'] Their presence may result in the mistaken diagnosis of meningococcic meningitis in cases in which smears are negative.

One notes several references to a gelatinous spinal fluid.[13] This phenomenon was strikingly apparent in the case reported; a dense jelly-like coagulum quickly formed, reducing the height of the cell count and protein level. Tolentino described the drawing out of a filament from the stylet of the spinal needle.[5r] The gelatinous consistency of the fluid may well be due to the presence of a high concentration of capsular polysaccharide. Nevertheless, the character of the fluid is generally not diagnostic and may vary from crystal-clear to green and yellow or may be frankly purulent.

12. Hoogerheide, J. C.: Studies on Capsule Formation: I. The Conditions Under Which Klebsiella Pneumoniae (Friedländer's Bacterium) Forms Capsules, J. Bact. **38**:367-389 (Oct.) 1939.

13. Footnote 5*j*, *r*, *b'*, and *c'*.

Table 3 reviews the various forms of specific treatment, excluding surgery, used in these cases. Too few patients have been treated with any one program of specific therapy to evaluate statistically its effectiveness. However, it would seem that use of sulfonamides has strikingly improved the prognosis from a 6.7% recovery rate to 45%. Of the sulfonamides, sulfadiazine has been shown to be the most effective in therapy of K. pneumoniae infections.[14] The paucity of cases in which treatment was with penicillin or streptomycin alone is attributed to the previous general indication of the effectiveness of sulfonamide therapy in purulent meningitis. Certainly, penicillin alone is of little value,[15] though isolated instances of its effectiveness in K. pneumoniae infections are recorded.[16]

K. pneumoniae is sensitive to streptomycin in vitro in concentrations as low as 0.625 γ of streptomycin per cubic centimeter of medium, though in the presence of blood or serum the tolerance of these micro-organisms to streptomycin may be increased 4 to 8 times.[17]

TABLE 3.—*Distribution of Therapy in All Reported Cases of K. Pneumoniae Meningitis*

	Deaths	Recoveries	Total Cases	Recoveries with Sequelae	Percentage Recovery
Presulfonamide era	56	4	60	2	6.7
Sulfonamides	11	9	20	0	45.0
Sulfonamides; penicillin	6	9	15	2	60.0
Penicillin (intramuscularly and intrathecally)	1	0	1	..	0.0
Sulfonamides; penicillin; streptomycin	6 *	7	13	1	53.8
Streptomycin	0	0	0	0	0.0
Sulfonamides; streptomycin	4 †	1	5	0	16.6
Penicillin; streptomycin	3	0	3	..	0.0
Sulfonamides; penicillin; streptomycin; chloramphenicol	0	1 ‡	1	0	100.0
Penicillin; streptomycin; aureomycin	0	1 §	1	0	100.0
Totals	87	32	119		

* Tartakoff and others [5j]: Recovery, then death of pulmonary embolism.
† Sadusk and others [5]: Improvement, then death of cardiac failure.
‡ Martin and Sureau, cited by Bombardier [5]: Recovery with chloramphenicol therapy after failure of sulfonamides, penicillin, and streptomycin.
§ Thompson and others: Aureomycin administered only initially.

Little streptomycin diffuses into the spinal fluid of normal persons after intramuscular injection.[18] After the daily intramuscular injections of 3 gm. of streptomycin for six days in a normal subject, but 1 unit of streptomycin per cubic centi-

14. Feinstone, W. H.; Williams, R. D.; Wolf, M. S.; Huntington, E., and Crossley, M. L.: The Toxicity, Absorption and Chemotherapeutic Activity of Sulfadiazine, Bull. Johns Hopkins Hosp. **67**:427-456 (Dec.) 1940.

15. Penicillin, report of the Council on Pharmacy and Chemistry, J. A. M. A. **125**:707 (July 8) 1944.

16. Kobacker, J. L., and Mehlin, G. B.: Klebsiella Pneumoniae Bacteremia Successfully Treated by Penicillin, Am. J. M. Sc. **210**:66-70 (July) 1945.

17. Footnote 5*b*. Heilman, F. R.: Streptomycin in the Treatment of Experimental Infections with Microorganisms of the Friedländer Group (Klebsiella), Proc. Staff Meet., Mayo Clin. **20**:33-39 (Feb. 7) 1945.

18. (*a*) Committee on Chemotherapeutics and Other Agents, National Research Council: Streptomycin in the Treatment of Infections, J. A. M. A. **132**:4-11 (Sept. 7) 1946. (*b*) Herrell, W. E., and Nichols, D. R.: Clinical Use of Streptomycin: Study of 45 Cases, Proc. Staff Meet., Mayo Clin. **20**:449-462 (Nov. 28) 1945.

meter of spinal fluid was detected. However, in a patient with Hemophilus influenzae meningitis to whom 1 gm. of streptomycin had been administered over a 24-hour period, 25 units of streptomycin per cubic centimeter of spinal fluid was detected. It is suggested that diffusion through the meninges is increased in the presence of inflammation.[19]

The route of administration of streptomycin in several of the cases under review was not recorded, so that an evaluation of the efficacy of treatment via the intrathecal as compared with other parenteral routes is not possible from these data.

K. pneumoniae is likewise highly sensitive to aureomycin, inhibition of the organism occurring at an aureomycin concentration of 0.3 γ per cubic centimeter of medium.[20] However, no cases of K. pneumoniae meningitis in which the whole or a part of the treatment was with aureomycin have been encountered in the literature. Aureomycin was not used for the total therapy in the case reported here, but a marked drop in temperature coincided with its administration.

Spinal fluid concentrations of aureomycin following the oral administration of the drug have been reported as negligible. Dowling and associates[21] detected aureomycin in only 1 among 17 specimens of cerebrospinal fluid of patients to whom 2 to 4 gm. of aureomycin had been administered orally. Levels of 0.03 to 0.06 γ were obtained three hours after the administration of 500 mg. intravenously. Such low spinal fluid levels are highly inconsistent with the increasing number of cases of meningitis of varying causation with favorable response to aureomycin therapy. These low levels have been shown to result from the instability of aureomycin at room temperatures and in blood or serum.[22] Modified assay techniques have revealed higher spinal fluid levels after oral aureomycin therapy. Lepper and others,[22a] using a modification of the Dornhouse technique, have detected concentrations of 0.13 γ per cubic centimeter in the spinal fluid of patients receiving 300 to 700 mg. of aureomycin orally a day. Maximum levels were reached on the third day of therapy.

Chloramphenicol (chloromycetin®) readily crosses the blood-brain barrier and appears in the cerebrospinal fluid after oral administration in concentrations ranging from 30 to 50% of levels noted in the blood stream.[23] The stability of the drug facilitates assay of levels. K. pneumoniae may be sensitive to as little as 0.6 γ of

19. Zintel, H. A.; Flippin, H. F.; Nichols, A. C.; Wiley, M. M., and Rhoads, J. E.: Studies on Streptomycin in Man: I. Absorption, Distribution, Excretion and Toxicity, Am. J. M. Sc. **210**:421-430 (Oct.) 1945.

20. Tunevall, G., and Frisk, A. R.: In Vitro Activity, Absorption and Excretion of Chloromycetin, Scandinav. J. Clin. & Lab. Invest. **2**:162-167, 1950.

21. Dowling, H. F.; Lepper, M. H.; Caldwell, E. R.; Whelton, R. C., and Brickhouse, R. L.: The Concentration of Aureomycin in Urine and Cerebrospinal, Pleural and Ascitic Fluids After Oral and Intravenous Administration, J. Clin. Invest. **28**:983-986 (Sept., Pt. 1) 1949.

22. (*a*) Lepper, M. H.; Dowling, H. F., and Brickhouse, R. L.: Blood and Cerebrospinal Fluid Concentrations of Aureomycin After Oral and Intramuscular Administration, J. Lab. & Clin. Med. **34**:366 (March) 1949. (*b*) Herrell, W. E., and Heilman, F. R.: Aureomycin: Studies on Absorption, Diffusion and Excretion, Proc. Staff Meet., Mayo Clin. **24**:157-166 (March 30) 1949.

23. Ross, S.; Bischoff, H.; Preisser, W., and Orr, W.: Some Observations on the Absorption and Excretion of Aureomycin and Chloramphenicol, abstracted, J. Clin. Invest. **28**:1050 (Sept., Pt. 1) 1949.

chloramphenicol per cubic centimeter of medium in vitro.[24] In the case of Martin and Sureau,[6] chloramphenicol therapy was described as effecting recovery after the failure of treatment with sulfonamides, penicillin, and streptomycin.

Terramycin has been shown to be effective in vitro against K. pneumoniae. After oral administration of 4 to 5 gm. daily, therapeutic spinal fluid levels are attained.[25] Insufficient clinical data are reported as yet concerning its effect in K. pneumoniae infections.

The importance of therapeutic spinal fluid levels of antibiotic is indicated by the work of Wood and Smith on surface phagocytosis.[26] Fully encapsulated K. pneumoniae bacilli were not phagocytized in vitro by leucocytes when the cells and organisms were incubated in a fluid medium devoid of antibody and devoid of surface against which the leucocytes could engulf the bacteria. The necessity of high levels of antibiotics to supplant the absent function of phagocytosis is obvious. The intrathecal administration of streptomycin in dosages of 100 mg. daily would seem indicated in this highly virulent infection.

The most consistently important factor in determining prognosis of K. pneumoniae meningitis appears to be the presence of the organisms in the blood. Of 44 cases in which results of blood cultures were recorded, they were positive in 32 and negative in 12. Seven, or 58.3%, of these patients with negative blood cultures survived. On the other hand, only five, or 15.6%, of those with positive blood cultures survived. Two of the patients with positive blood cultures were convalescent from meningitis when they died of unrelated cardiovascular disease. Two of the patients with positive blood cultures who survived were treated before the advent of specific therapy. The precise combination of therapeutic agents actually responsible for recovery in those patients who received specific therapy is not apparent.

Certainly, the severity and course of the debilitating state which is so frequently associated with this disease are important factors influencing prognosis. In this period of rapidly advancing antibiotic therapy it is not possible at this time to evaluate the recovery rate from the various regimens that have been proposed. The therapeutic outlook, however, has brightened considerably.

SUMMARY AND CONCLUSIONS

Klebsiella pneumoniae (Friedländer's bacillus) meningitis is infrequent. One hundred eighteen cases have been collected from published reports.

A case of K. pneumoniae meningitis with bacteremia and pneumonia, with recovery on penicillin, aureomycin, and streptomycin therapy is reported.

The most frequent K. pneumoniae infections associated with meningitis are those of the ears, the upper and lower respiratory tract, and wounds. In infants the primary focus is most frequently undetermined.

24. Ross and others.[28] Hewitt, W. L., and Williams, B.: Chloromycetin (Chloramphenicol) in the Treatment of Infections, New England J. Med. **242**:119-128 (Jan. 26) 1950.

25. Werner, C. A.; Knight, V., and McDermott, W.: Absorption and Excretion of Terramycin in Humans: Comparison with Aureomycin and Chloramphenicol, Proc. Soc. Exper. Biol. & Med. **74**:261-267 (June) 1950.

26. Wood, W. B., and Smith, M. R.: Surface Phagocytosis: Its Relation to the Mechanism of Recovery in Acute Pneumonia Caused by Encapsulated Bacteria, Tr. A. Am. Physicians **60**:77-81, 1947.

Diabetes mellitus is associated with K. pneumoniae infections beyond its expected occurrence in random population groups. The presence of glycosuria and ketosis during the acute stages of the disease, however, does not necessarily indicate true diabetes mellitus.

No definitive clinical characteristics distinguishable from those of other forms of purulent meningitis are evident. A gelatinous spinal fluid sometimes occurs. Petechiae have been noted.

Streptomycin, aureomycin, chloramphenicol, and terramycin all exert an antibacterial effect upon most strains of K. pneumoniae. Which of these drugs is most effective in the treatment of K. pneumoniae meningitis remains to be determined.

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FURTHER STUDIES ON THE RELATIONSHIP OF S_f 10-20 LIPOPROTEIN MOLECULES TO ATHEROSCLEROSIS

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WE HAVE previously presented evidence relating certain lipoprotein molecules of the serum of human beings and experimental animals with the development of atherosclerosis.[1] It is the purpose of this report to evaluate a clinical follow-up study which has further amplified this relationship.

The basic premise of this research was that there might be a defect in the molecules which transport fats and cholesterol that could be more intimately related to the pathogenesis of atherosclerosis than are the total analytical levels of the various lipids themselves, e. g., serum cholesterol levels. Since cholesterol, its esters, neutral fat, and phospholipids are all transported in the blood via giant lipoprotein molecules, it was necessary to develop a technique for measuring both the types and the concentration of lipoproteins present in a small sample of blood from an individual patient. The ultracentrifuge has proved highly useful for this purpose. In the ultracentrifuge, under specified conditions,[1c] each independent lipoprotein molecular species is characterized by its flotation rate. Since there are several different lipoproteins present, very similar in chemical structure, it has been found useful to name the individual species by their flotation rates in Svedberg units. Thus, if a molecule migrates in the ultracentrifuge with a rate of 20 units, it is referred to as a molecule of the S_f 20 class (S_f = Svedberg units of flotation).

Our previously reported work has shown that those lipoproteins migrating with rates between 10 and 20 Svedberg units (the S_f 10-20 class of lipoproteins) are associated with human atherosclerosis.

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Read before the Section on Internal Medicine at the One Hundredth Annual Session of the American Medical Association, Atlantic City, June 13, 1951.

1. (*a*) Gofman, J. W., and others: Science **111**:166, 1950. (*b*) Gofman, J. W.; Jones, H. B.; Lindgren, F. T.; Lyon, T. P.; Elliott, H. A., and Strisower, B.: Circulation **2**:161, 1950. (*c*) Gofman, J. W.; Lindgren, F. T.; Jones, H. B.; Lyon, T. P., and Strisower, B.: J. Gerontology **6**:105, 1951.

The evidence supporting the relationship of these molecules with atherosclerosis in the human being may be briefly summarized as follows:

A. The presence and concentration of these molecules of the S_f 10-20 class in presumably normal persons parallel well and are consistent with the clinical occurrence of atherosclerosis in such persons.

1. Children show much lower average concentrations of S_f 10-20 molecules than do adults.

2. The young adult females show much lower average levels of S_f 10-20 molecules than do adult males of corresponding age.

3. Both sexes show an increase in concentration of S_f 10-20 molecules with aging, especially marked in the transition from the third to the fourth decade of life.

4. The difference between the lipoprotein concentrations of the male and of the female becomes progressively obliterated with age in the fifth and sixth decades of life.

B. The molecules of the S_f 10-20 class are present in higher average concentration and show a greater frequency of elevated levels in patients with proved myocardial infarction or with angina pectoris. In fact, in all 15 subjects with myocardial infarction who came to autopsy, moderate to advanced coronary atherosclerosis was present. The S_f 10-20 level in these patients was one and one-half times higher than in the myocardial infarction group as a whole and more than two times as high as in normal subjects. Inasmuch as over 90% of cases of myocardial infarction and angina pectoris have as their basis coronary artery atherosclerosis, the elevated S_f 10-20 lipoprotein levels in such cases is strong evidence linking them with atherosclerosis of at least this vascular bed.

C. The S_f 10-20 lipoprotein levels are much higher in the hypertensive patient manifesting overt coronary artery disease than in hypertensive patients who have not yet shown such clinical manifestations.[1e]

D. The S_f 10-20 lipoprotein levels are higher in diabetic patients manifesting vascular disease than in diabetic patients without overt vascular disease.[1e]

E. The S_f 10-20 lipoprotein levels are greatly elevated in a group of syndromes and diseases associated with premature and excessive atherosclerosis, among which are (1) the nephrotic syndrome, (2) myxedema, (3) xanthoma tuberosum, and (4) familial hypercholesteremia.

Although certain of the above categories of disease show frankly elevated serum cholesterol levels, a large proportion of patients with atherosclerosis display serum cholesterol levels overlapping those of the "normal" population. However, at any range of serum cholesterol, even including hypercholesteremia, the patients with atherosclerosis or diseases predisposing to atherosclerosis show higher S_f 10-20 levels than do presumably normal persons. For example, at a low cholesterol level, such as 200 to 225 mg. per 100 cc., patients with coronary disease show higher average S_f 10-20 levels than do normal persons. Likewise, in the hypercholesteremic range, 300 to 350 mg. per 100 cc., patients with coronary disease show higher S_f 10-20 levels than do normal persons who have the same total cholesterol value. This relationship holds for any cholesterol range (see Table 1).

Having established an association of the S_f 10-20 molecules with atherosclerosis, we were interested in determining whether the serum level of such molecules actually influences clinically the further progression of atherosclerotic disease. During the past one and a half years a clinical follow-up study has been in progress to determine the prognostic import of high S_f 10-20 levels and the prophylactic and therapeutic potentialities of reducing the S_f 10-20 levels in patients with manifestations of atherosclerosis. Certain conclusions can be drawn from the accumulated clinical and laboratory evidence presented below.

TABLE 1.—*Relationship of S_f 10-20 Levels to Serum Cholesterol Levels in Normal Persons and in Patients with Coronary Artery Disease (Age Group, 40 to 60 Years)*

	Serum Cholesterol Range, Mg./100 Cc.	200-219	220-239	240-259	260-279	280-299	300-349	350-399	400-500	Total
Number	Cor.	11	14	19	25	19	38	17	8	151
	Norm.	30	65	61	38	32	40	17	3	286
% above 60 mg./100 cc.	Cor.	36	50	57	52	63	71	71	88	Average 62
	Norm.	20	7	26	26	44	42	52	33	27
	Ratio C/N	1.8	7.1	2.1	2.1	1.4	1.7	1.4	2.6	2.2
% below 60 mg./100 cc.	Cor.	64	50	43	48	37	29	29	12	38
	Norm.	80	93	74	74	56	58	48	67	73
	Ratio C/N	0.76	0.55	0.58	0.66	0.66	0.50	0.58	0.18	0.52

TABLE 2.—*Percentage of Cases Above Given S_f 10-20 Level*

Level, Mg./100 Cc.	Nonrecurrences, %	Recurrences, %
120	2	4
100	3	8
80	16	39
60	47	73
45	83	100
30	95	100

Average S_f 10-20 level in recurrences..... = 78 mg./100 cc. (σ_m* = 2.2)
Average S_f 10-20 level in nonrecurrences..... = 60 mg./100 cc. (σ_m = 5.8)
Difference = 18 mg./100 cc. (σ diff.† = 6.4)

* Standard error of mean.
† Standard error of difference.

RECURRENCE OF MYOCARDIAL INFARCTION

In a group of patients who have experienced one or more myocardial infarctions, it would be anticipated that early recurrence of myocardial infarction would be more probable in those persons with the greatest degree of atherosclerotic activity. If the serum level of S_f 10-20 molecules reflects the degree of atherosclerotic activity, then those patients who maintain higher average levels might be expected, statistically, to show earlier recurrence of myocardial infarction.

A representative group of 100 patients with previous myocardial infarction whose blood was studied repeatedly during a period of 12 to 18 months beyond their first blood study and who have not had any recurrences of myocardial infarction is compared with a group of 26 patients who experienced a recurrent myocardial infarction during this period of study. For this purpose patients are

classified on the basis of the integrated average level of S_f 10-20 lipoproteins during the observation period, independent of any dietary or drug regimen they followed. Thus, it is felt that the only major factor operative should be the S_f 10-20 lipoprotein level. The data comparing patients experiencing recurrence with those not having recurrent infarctions are given in Table 2.

The data in Table 2 show that both the average blood level of S_f 10-20 molecules and the frequency of occurrence of high levels (over 60 mg. per 100 cc.) are significantly ($P = 0.03$) greater for the patients experiencing recurrent infarction than for those who did not have a recurrence. Further, while none of the recurrence group showed levels below 45 mg. per 100 cc., there was 17% of the nonrecurrence group below this level. This difference is highly significant ($P = 0.02$).

These observations are then supportive to the hypothesis that patients with coronary artery disease who maintain high levels of S_f 10-20 lipoproteins are more likely to have complications as a result of progression of their disease than are those whose levels are lower.

TABLE 3.—*Blood Levels of S_f 10-20 Lipoproteins in Twenty-Three Patients Studied During the Acute Phase Who Survived and in Twenty-Six Patients Studied During the Acute Phase Who Died*

Level of S_f 10-20, Mg./100 Cc.	Survived, % Cases Above Given Level	Died, % Cases Above Given Level
95	0	25
80	0	50
60	25	75

PATIENTS STUDIED DURING THE ACUTE PHASE OF MYOCARDIAL INFARCTION

At the outset of our studies of the relationship of S_f 10-20 lipoproteins to atherosclerosis, patients were not studied unless they were at least six weeks beyond their myocardial infarction. However, recently we have accumulated data during the acute phase (during first week after occurrence or on autopsy blood). From the data in Table 3 it appears that important differences exist between those patients studied during the acute phase who survive and those studied during the acute phase who die.

These data show that the prognosis for patients with acute myocardial infarction is markedly poorer if they have highly elevated S_f 10-20 levels. This may reflect the severer degree of over-all coronary atherosclerosis in the group which fails to survive. Further, it appears that the survivors generally show a rise in levels after the acute phase is passed. Thus, possibly the metabolic capability of reduction in level during the acute episode may be of value to the patient.

INFLUENCE OF DIET AND S_f 10-20 LEVEL ON OCCURRENCE OF MYOCARDIAL INFARCTION IN PATIENTS ALREADY HAVING CORONARY DISEASE

We have been able to show in carefully controlled groups of patients at a hospital diet table that a low-fat, low-cholesterol diet will effect a reduction in the S_f 10-20 lipoprotein level in the majority of cases (50% reduction). The possible therapeutic value of such reduction has been tested in a group of ambulatory patients

with known coronary artery disease. From our total experience, 38 patients with either angina pectoris or previous myocardial infarction, or both, have had a new episode of proved myocardial infarction during the period of follow-up. These cases may be compared with two "control" groups:

Group 1 (*a*) and (*b*) was composed of two series of patients with coronary disease who had not had any new episode of infarction during the one-year follow-up period, and who were matched patient for patient on the basis of identical initial S_f 10-20 levels. The matched controls were blindly selected at random.

Group 2 was a series of patients with coronary disease chosen as was Group 1 *a* and *b* to match the levels of the recurrence group, except that all patients of series *b* had been advised and had claimed moderate to strict adherence to a low-fat, low-cholesterol diet.

The results are presented in Table 4.

TABLE 4.—*Comparison of S_f 10-20 Lipoprotein Levels of Recurrent and Nonrecurrent Cases in a One-Year Follow-Up Study*

		Over-All Group				
	No. of Cases	Initial Level, Mg./100 Cc.	Integrated Level During Period of Study, Mg./100 Cc.	Average Reduction in % of Initial Level, %	Upper 50% of Cases: Average Reduction, %	Lower 50% of Cases: Average Reduction, %
Matched Group (Series 1a)						
Recurrences	38	87.3	81.9	6	9	1
Nonrecurrences	38	87.1	68.0	22	29	10
Matched Group (Series 1b)						
Recurrences	33	82.8	78.2	5.5	7.8	1
Nonrecurrences	33	81.4	71.5	14	17.3	3
Matched Group (Group 2) Recurrences vs. nonrecurrences in which all of nonrecurrence group were on diet						
Recurrences	36	84.0	79.8	5	7.7	1
Nonrecurrences	36	83.8	63.4	24.4	34	7.5

The following conclusions can be drawn from these data:

A. Comparing representative samples of our over-all nonrecurrence population with coronary disease, chosen at random between dieters and nondieters, with those patients having recurrent infarctions, it is seen that the nonrecurrence group is associated with a significantly greater reduction in S_f 10-20 levels than the recurrence group.

B. Comparing a representative sample of our nonrecurrence group who had been advised to follow a low-fat, low-cholesterol diet with patients having recurrent infarction, it is seen that there is an even greater reduction in S_f 10-20 level in the nonrecurrence group than in the recurrence group.

C. In all groups dietary reduction of S_f 10-20 levels is significantly greater in patients with high levels (upper half of total group) than in patients with lower levels (lower half of group).

D. The reductions observed here over the 10- to 18-month period are much less than those seen in our closely controlled dietary experiments in which total fat intake is maintained between 25 and 50 gm. per day. However, the above data represent what can be achieved in an average cross section of patients following a low-fat, low-cholesterol diet at home.

Since the recurrence group and the various nonrecurrence groups are essentially comparable in initial S_f 10-20 level, previous medical history, and age, and since the only therapeutic measure used to reduce the S_f 10-20 level was the low-fat, low-cholesterol diet, it is apparent that the patients who have fared best are those who have shown the greater dietary reduction of S_f 10-20 levels. It was shown above that recurrence is more likely at high S_f 10-20 levels than at low levels, and further that patients with high levels show greater dietary drops in level than those with lower levels. Thus, it is seen that the moderate reductions produced by diet are capable of giving these persons significant protection from a high recurrence rate of myocardial infarction. All these data are consistent with the hypothesis that the reduction in S_f 10-20 lipoprotein level may have lessened the progression of atherosclerotic disease.

Further, it was noted that the patients with coronary disease in the dietary group who had previously had angina pectoris showed progressive improvement with respect to this symptom over the period of study, as measured by decreased glyceryl trinitrate requirement and increased occupational work tolerance. This was not observed in the nondietary group.

PHARMACOLOGIC AGENTS AFFECTING THE S_f 10-20 LIPOPROTEIN LEVELS

The most striking effects upon lipoprotein levels are produced by the action of heparin given parenterally. Heparin acts both in the rabbit and in the human being to shift the lipoproteins of high S_f classes into those of successively lower classes. Thus, reduction in the S_f 20-100 and S_f 10-20 lipoproteins can be maintained for periods of several hours to days in the human being and rabbit, depending upon the mode of injection of heparin.

The alterations in lipoprotein levels produced by heparin in the rabbit are favorable, in that the rabbits receiving intermittent heparin injections during cholesterol feeding experiments show definite suppression of development of atherosclerosis.[2]

As yet, no human patients have failed to show acute shifts in the lipoproteins under the influence of heparin, although there is great variability in the duration of the effect on the blood picture. Clinically, it has been noted that in 30 of 32 patients with typical angina pectoris there was either dramatic reduction or complete relief of angina for periods of 3 to 10 days following each single intravenous injection of 25 to 100 mg. of heparin.[3]

SUMMARY

The class of lipoproteins in human blood designated as the S_f 10-20 class, which has previously been reported to be associated with atherosclerosis, has now been studied in a large group of patients with coronary artery disease over a one to one and one-half year period.

2. Graham, D.; Lyon, T. P.; Gofman, J. W.; Jones, H. B.; Yankley, A., and Simonton, J.: Circulation **4**:666, 1951.

3. The general effect could be prolonged by administration of repository heparin. Heparin for intravenous and repository injection was supplied by Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

Recurrence of myocardial infarction in patients with previous infarcts, and occurrence of infarction in patients with angina pectoris, developed predominantly in that part of the group showing the highest S_f 10-20 concentrations over the period of observation.

Low-fat, low-cholesterol dietary management of patients with coronary artery disease was effective in reducing average S_f 10-20 levels. This reduction in S_f 10-20 levels was associated with a marked reduction in rate of occurrence of new myocardial infarctions in the group.

Heparin suppresses the rise in concentration of S_f 10-50 molecules in the cholesterol-fed rabbit and minimizes the development of atherosclerosis.

Heparin produces similar alterations in the lipoproteins of the human subject.

Clinically, administration of 20 to 100 mg. of heparin produced dramatic relief of angina pectoris in 30 of 32 patients for periods of 3 to 10 days following a single injection.

Case Reports

BACILLARY DYSENTERY DUE TO SHIGELLA ALKALESCENS

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DYSENTERY due to Shigella alkalescens is still not a reportable disease in many parts of the United States. This is regrettable since S. alkalescens is a true member of the Shigella group with all its epidemiologic implications. It produces the characteristic intestinal lesions of bacillary dysentery. The fact that the disease may occur in a mild form does not detract in the least from its potential dangers. In children and some adults severe intestinal and renal infections may result.

HISTORICAL STUDIES

The history of S. alkalescens infections parallels that of Sonne-Duval dysentery. The latter, originally described by Duval in 1904, was not accorded its proper clinical significance until Sonne's work in 1914. Since then, undoubted evidence of its pathogenicity has been presented. The same historical evolution appears to be taking place in the case of S. alkalescens. Originally described by Andrewes in 1918,[1] properly documented evidence of its pathogenicity has been offered by Smith and Fraser (1928),[2] Weil (1929),[3] Popoff and Spanswick (1931),[4] Bamforth,[5] Mackenzie and Ratner,[6] Murray and Pike,[7] Starkey (1934),[8] Snyder and Hanner (1937),[9] Neter and Rappole,[10] Wooley and Sweet,[11] and Neter (1938).[12] These

From the Dysentery Registry, The Bronx Hospital.

1. Andrewes, F. W.: Dysentery Bacilli: The Differentiation of the True Dysentery Bacilli from Allied Species, Lancet **1**:560, 1918.

2. Smith, J., and Fraser, A. M.: A Case of Continued Fever Due to B. Alkalescens (Andrewes), J. Path. & Bact. **31**:511, 1928.

3. Weil, A. J.: Ueber den Bazillus alcalescens (Andrews), Zentralbl. Bakt. (Abt. 1) **112**:376, 1929.

4. Popoff, N. W., and Spanswick, M. P.: A Case of Pyelonephritis of Pregnancy Due to Eberthella Alkalescens, J. Lab. & Clin. Med. **16**:437, 1931.

5. Bamforth, J.: Enquiry into Coli Anaerogenes Bacteria, J. Hyg. **34**:69, 1934.

6. Mackenzie, D. W., and Ratner, M.: Bacillus Alkalescens Pyelonephritis with Blood Infection: Review of Literature and Report of Case with Recovery, J. Urol. **31**:671, 1934.

7. Murray, M. F., and Pike, R. M.: Acute Pyelitis Due to Shigella Alkalescens, Clin. Misc., Mary I. Bassett Hosp. **1**:68, 1934.

8. Starkey, D. H.: Case of B. Alkalescens (Andrewes) Bacteraemia with Serological Confirmation, Canad. M. A. J. **31**:42, 1934.

9. Snyder, M. L., and Hanner, T. P.: Bacilluria Caused by Bacterium Alkalescens, J. Infect. Dis. **60**:51, 1937.

10. Neter, E., and Rappole, F.: Pathogenicity and Antigenic Structure of Shigella Alkalescens (Andrewes), Arch. Path. **25**:298 (Feb.) 1938.

reports have been concerned largely with infections of the urinary tract. In 1928 Smith and Fraser [2] reported a case of puerperal fever in a woman with diarrhea. A positive blood culture for S. alkalescens was obtained, and the authors regarded the infection to be of intestinal origin. In 1934 Welch and Mickle [13] described two outbreaks of bacillary dysentery due to S. alkalescens among students and nurses. The source of infection was a food handler, and the outbreak terminated promptly with removal of the food handler. Welch and Mickle felt that the organism was capable of producing disease in man and should be included in the Shigella group. Further reports concerning the pathogenicity of S. alkalescens pointing to intestinal and occasional simultaneous genitourinary involvement appeared by Mackenzie and Ratner,[6] Starkey (1934),[8] Brown and Anderson (1936),[14] Snyder and Hanner (1937),[9] Wooley and Sweet (1938),[11] Pio de Roda,[15] de Assis,[16] Neter,[17] Snyder,[18] Cooper and co-workers,[19] Nabarro and Edward (1939),[20] and Felsen and Wolarsky (1940).[21] The last-named authors reported a group of 14 cases, viz., 3 of acute bacillary dysentery, 1 of chronic distal (regional) ileitis, 7 of chronic ulcerative colitis, and 3 of doubtful significance.

PERSONAL OBSERVATIONS

Since 1940 we have encountered numerous instances of S. alkalescens dysentery. Within the past three months we have seen three patients, two adults and a boy of 14 years, with the acute form of the disease. The adults were food handlers, one working in our own nursery and discovered during a routine monthly check-up by the hospital epidemiologist. Two of the three consented to sigmoidoscopy and exhibited the characteristic three-stage progression of pathological intestinal changes, purulent mucosal exudate as shown cytologically, and mucosal crypt aspiration cultures positive for S. alkalescens. It is our own impression that this type of

11. Wooley, P. V., and Sweet, M.: The Significance of Shigella Alkalescens (Andrewes), J. Pediat. **12**:596, 1938.

12. Neter, E.: Infections of the Urinary Tract Due to Shigella Alkalescens, J. Urol. **39**:727, 1938.

13. Welch, H., and Mickle, F. L.: Relationship of Shigella Alkalescens to Other Members of Shigella Group, Am. J. Pub. Health **24**:219, 1934.

14. Brown, M. H., and Anderson, E. A.: B. Alkalescens (Andrewes): Its Relation to Members of Typhoid-Dysentery Group, Canad. Pub. Health J. **27**:560, 1936.

15. Pio de Roda, A.: The Bacteriology of Ileocolitis and Diarrheas Among Children, J. Philippine Islands M. A. **19**:73, 1939.

16. de Assis, A.: Estudos sobre Shigella alcalescens Andrewes, Hospital, Rio de Janeiro **15**:447, 1939.

17. Neter, E., and Gilfillan, S.: Agglutinins for Shigella Alkalescens in Sera of Normal Human Individuals and of Patients With and Without Shigella Alkalescens Infections, Am. J. Hyg. **29**:67, 1939.

18. Snyder, M. L.: Bacterium Alkalescens in Stools of Normal Infants, J. Pediat. **14**:341, 1939.

19. Cooper, M. L.; Furcolow, M. L.; Mitchell, A. G., and Cullen, G.: The Relation of Dysentery to the Acute Diarrhea of Infants and Children, J. Pediat. **15**:172, 1939.

20. Nabarro, D., and Edward, D. G. F.: Pathogenicity of Bacterium Alkalescens, J. Path. & Bact. **49**:515, 1939.

21. Felsen, J., and Wolarsky, W.: Bacillary Dysentery Due to Bacillus Alkalescens, New York J. Med. **40**:1303, 1940.

dysentery either is on the increase or is being diagnosed more accurately. No reliable statistical data are available on this point, since the disease is not generally reportable.

COMMENT

S. alkalescens infections present two interesting features in addition to the intestinal manifestations. These are frequent infections of the urinary tract and occasional positive blood cultures. The latter are extremely rare in other types of Shigella infection and usually become sterile in S. alkalescens infections when the postive intestinal cultures disappear. Up to the present writing, we have encountered, in addition to the usual type, the following atypical forms of dysentery due to S. alkalescens: appendicular, afebrile, constipated, and asymptomatic. Thus far, we have not seen the pneumonic, meningitic, or agranulocytoid types.[22] It is significant that the atypical forms are apt to be important factors in spreading the disease, since they are rarely diagnosed except during outbreaks. They exhibit the same intestinal lesions at sigmoidoscopy as the typical cases. For these reasons every contact in a case of S. alkalescens infection should receive the benefit of fecal cultures just as in other Shigella infections or typhoid. Laxity in reporting the disease and procrastination in handling it may lead to a repetition of conditions existing in 1937, when bacillary dysentery was actually not reportable in 15 of our states. By 1941, through the cooperation of the Dysentery Registry and public-health officials, it was made reportable in every state. It is incumbent upon us now to see that S. alkalescens dysentery is likewise included among the reportable dysenteries.

S. alkalescens, like other members of the Shigella group, is sensitive to terramycin and chloramphenicol (chloromycetin®). Sulfadiazine, sulfathiazole, and succinylsulfathiazole (sulfasuxidine®) are also valuable therapeutic agents.

SUMMARY

Bacteriological, pathological, and clinical data indicate that Shigella alkalescens is a true member of the Shigella group. The disease should be treated as a true bacillary dysentery and be made universally reportable.

22. For this reference and more detailed bibliography on the dysenteries, see Felsen, J.: Bacillary Dysentery, Colitis and Enteritis, Philadelphia, W. B. Saunders Company, 1945.

ACUTE HEMOLYTIC ANEMIA ASSOCIATED WITH MYELOID METAPLASIA OF THE SPLEEN

Report of a Case Treated by a Splenectomy

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SINCE the description of Jackson and associates [1] of myeloid metaplasia, there have been numerous case reports concerning this disease in its primary and secondary forms. These cases have been divided into two predominant groups: the one resulting from bone marrow replacement on the basis of malignant growth or fibrosis, the other being primary or agnogenic. It has been reported in association with carcinoma metastatic to bone and with infectious states, such as scarlet fever, and in cases of generalized sepsis, tuberculosis of spleen, and idiopathic osteosclerosis. It has frequently been reported as bearing relationship to acquired hemolytic anemia. Those cases showing clinical and laboratory evidence of hemolytic anemia have been, as far as we have been able to ascertain, without exception chronic.[2] We have recently had occasion to observe a case with microscopic evidence of marked myeloid metaplasia of the spleen and exhibiting an acute clinical course characterized by marked hemolysis and severe anemia. Because no case of this sort has been reported previously, because of the acute nature of the illness and the diagnostic problems presented by the confusing clinical course, because of the poor postsplenectomy prognosis [3] in cases of myeloid metaplasia as compared with the relatively good one in cases of acquired or idiopathic hemolytic anemia, and because this case presents many hematologic aspects in which it differs from other cases, we believe that it should be reported.

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Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Jackson, H., Jr.; Parker, F., Jr., and Lemon, H. M.: Agnogenic Myeloid Metaplasia of the Spleen: A Syndrome Simulating Other More Definite Hematologic Disorders, New England J. Med. **222**:985-994, 1940.

2. (*a*) Jackson and others.[1] (*b*) Thompson, W. P., and Illyne, C. A.: Clinical and Hematologic Picture Resulting from Bone Marrow Replacement, M. Clin. North America **24**:841-853, 1940. (*c*) Block, M., and Jacobson, L.: Myeloid Metaplasia, J. A. M. A. **113**:1390-1396 (Aug. 19) 1950. (*d*) Levinson, S. A., and Limarzi, L. R.: Agnogenic Myeloid Metaplasia of the Spleen: Report of a Case with Necropsy Findings, Am. J. Clin. Path. **17**:449-461, 1947. (*e*) Jordan, H. E., and Scott, J. K.: Case of Osteosclerosis with Extensive Extramedullary Hemopoiesis and Leukemic Blood Reaction, Arch. Path. **32**:895-909 (Dec.) 1941.

3. Block and Jacobson.[2c] Reich, C., and Rumsey, W., Jr.: Agnogenic Myeloid Metaplasia of Spleen: Report of 5 Cases Illustrating Diagnostic Difficulties and Danger of Splenectomy and Radiation Therapy, J. A. M. A. **118**:1200-1204 (April 4) 1942.

PATHOGENESIS [4]

In certain pathologic conditions, hematopoiesis may be observed in organs of the body which under normal conditions form no myeloid tissue. This is called myeloid metaplasia or extramedullary or ectopic myelopoiesis. It appears frequently in organs which generate myeloid elements in the embryo, namely, the spleen, lymph nodes, liver, thymus, and adrenal glands. At first neutrophils and myelocytes appear, and subsequently megakaryocytes and erythroblasts are seen. Local extramedullary myelopoiesis may occur in areas of pathologic calcification, such as calcified arterial plaques. It may also occur in regional lymph nodes as a result of local infection, in benign tumors, and in the renal pelvis. Extramedullary myelopoiesis may result from infectious diseases, toxic states, and diseases of blood-forming organs, above all, myelogenous leukemia. Changes of the liver are characterized by circumscribed cell foci or by diffuse obstruction of the capillaries by blood elements. In the spleen and lymph nodes the myeloid transformation is confined to the pulp. There are three outstanding theories of the histogenesis of myeloid metaplasia:

1. The colonization theory holds that preerythroblasts and myelocytes are swept from the bone marrow by the blood stream into foreign situations, where they become lodged, propagate, and mature. This idea has been largely abandoned.

2. The theory of local formation, which postulates the autochthonous formation of myeloid elements from fixed local cells of the affected tissues, is a natural corollary to Piney's theory regarding the spleen as a bipartite organ, being essentially a lymphatic structure but retaining myeloid potentialities.

3. Maximow [4b] has a further thesis of differential development of cells, maintaining that embryological connective tissue throughout the body is capable of giving rise to cells which under normal conditions are formed only in the bone marrow of the adult. Under abnormal conditions, however, these tissues may regain their embryonic capacity for producing myeloid cells.

REPORT OF CASE

The patient was a 30-year-old white man, whose chief complaint was fever and headache for two weeks. The history of the present illness was as follows: Two weeks prior to admission, the patient had a frontal headache which became progressively worse and was particularly marked in the three days prior to admission. For the two weeks prior to admission, he had a temperature elevation averaging 101 to 102 F. Three days before admission, he noticed jaundice of the skin and of the sclerae. Three or four days before admission, he vomited a yellow material but said that he had taken yellow capsules and tablets, and the vomiting usually occurred after taking the medicine. One week before admission, a sore throat developed which lasted three or four days and was moderate in severity. He had no chest pain, no nuchal rigidity, no abdominal pain, and no diarrhea. For three or four days he had been somewhat constipated, but he had noticed no change in the color of his stool. For one week before admission, his urine had been dark, but he noticed that it became lighter on the day before admission. There was no hematuria or dysuria. There was no family history of icterus, and the patient had never had a similar attack previously. One to two days before admission, he was given two injections of a liver preparation by an outside physician. The patient worked

4. (*a*) Jordan, H. E.: Extramedullary Blood Production, Physiol. Rev. **22**:375-384, 1942. (*b*) Maximow, A.: The Relation of Blood Cells to Connective Tissues and Endothelium, ibid. **4**:533-563, 1924. (*c*) Lang, F. J.: Myeloid Metaplasia, in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, Vol. 3.

in a garage as a painter and used spray paints frequently. He did not smoke and drank rarely. There was no history of rheumatic fever; his family history was noncontributory, and the review of systems otherwise gave normal results.

Results of Physical Examination.—The blood pressure was 122/54. The temperature was 103 F. The pulse rate was 130. The patient was a well-developed, well-nourished, young white man, who appeared acutely ill and was complaining of headaches. He appeared definitely icteric. The head and neck were normal. There was no nuchal rigidity. Icterus of the sclerae was noted. The mucous membranes of the mouth and throat were pale, as were the conjunctivae. There was a Grade II systolic murmur at the apex. There were no organs or masses palpable in the abdomen. Peristalsis was normal. There was moderate icterus of the skin, and neurological examination gave normal results.

Laboratory Work.—On admission, Aug. 22, 1950, the red blood cell count was 1,200,000, and the white blood cell count, 4,400, with 76% polymorphonuclear cells. Hemoglobin content was 4 gm. per 100 cc. The icterus index was 18. The urine was normal and serologic reactions were negative. Routine agglutinations were normal. The Coombs test gave a negative reaction. Results of cold agglutinations were negative. Red cell fragility was normal. Gastric acidity showed 13 degrees of free hydrochloric acid after an alcohol test meal. The icterus index on the day following admission was 18. On Aug. 24, thrombocytes (platelets) were 170,000 and reticulocytes 0. The icterus index on Aug. 29 was 28. The sulfobromophthalein (bromsulphalein®) sodium test showed 16% retention in 45 minutes. The thymol turbidity was 4 units. The direct van den Bergh reaction was 0.4 mg. per 100 cc., and the indirect, 6.3 mg. Cephalin flocculation was 2+. Fecal urobilinogen was 14 Ehrlich units per 100 gm. The reticulocyte count remained at 0 until Aug. 30, at which time the count was 2; it reached a maximum of 6 on Aug. 31. At this time, the patient was receiving vitamin B_{12} and had also been given many transfusions. The prothrombin time on Sept. 7 was 50% of normal. On Sept. 12 the icterus index was 7; on Sept. 13, 14; on Sept. 18, 10, and on Sept. 22, 5. Blood cultures were negative. A bone marrow biopsy specimen showed megaloblastic proliferation but was not diagnostic. A chest roentgenogram and roentgenograms of the long bones were normal. An electrocardiogram taken on Aug. 23 showed no abnormality.

Hospital Course.—By the fourth or fifth hospital day, the spleen was definitely palpable, extending 2 or 3 fingerbreadths below the costal margin. It was soft and nontender. The liver was at no time palpable, however. After blood for the patient's initial laboratory work had been drawn and the initial sternal marrow biopsy was done, the patient was transfused. Transfused blood was hemolyzed almost as fast as it was given to him. His icterus index continued to rise, and, although he at one time was given sufficient blood to bring the hemoglobin concentration to 14.5 gm., within 24 hours, it had dropped to 13 gm., and the surgeons were contacted. Splenectomy was recommended. On Sept. 7 a large, friable spleen and accessory spleen were removed. The patient withstood the operative procedure well. Microscopic diagnosis of the spleen was congestive splenomegaly, with infarction and marked erythroid and myeloid metaplasia. A biopsy specimen of the liver taken at the time of surgical intervention showed mild periportal lymphocytic infiltration. The patient received 500 cc. of blood during the surgical procedure and was not transfused thereafter. The postoperative course was relatively smooth, the wound healing with normal rapidity.

Before surgical treatment, he had received vitamin B_{12} for a few days, along with the transfusions, on the assumption that the condition might be a pernicious anemia, but the effect of the vitamin B_{12} was obfuscated by the transfusions and the continued hemolysis. Postoperatively, the patient's icterus index dropped to normal. He ran a low-grade fever for approximately two weeks, subsequently was afebrile, and showed evidence of clinical and hematologic improvement. By Sept. 22 the red blood cell count was 4,100,000, the white blood cell count 6,200, with 78% polymorphonuclear cells. The hemoglobin concentration was 11.5 gm., the hematocrit, 39%, and thrombocytes, 300,000. Since he was asymptomatic, he was sent home on pass. Since that time, he has returned at monthly intervals and his condition has shown continuing improvement. His final white blood cell count on Dec. 12, 1950, was 8,700; the hemoglobin concentration was 97%; the reticulocyte count, 1.2%, and the sedimentation rate, 2 mm. in one hour. The urine and the results of liver-function tests were normal. The bone marrow on examination, Dec. 31, 1950, was normal.

COMMENT

The clinical and histopathologic aspects of myeloid metaplasia have been well covered by Block and Jacobson and others.[5] They are presented again here partially in the nature of a review and partially to form a basis for comparison with the case under consideration. Except for those cases in which myeloid metaplasia was associated with polycythemia vera or followed it, anemia was the predominant part of the picture. The anemia was moderate or severe. The white blood cell count was extremely variable and covered the range from leucopenia to levels of marked leucocytosis. Most cases have shown thrombocytopenia. One of the prime diagnostic features of myeloid metaplasia is the appearance on smear of the peripheral blood. At the same time, immature forms of white blood cells are almost invariably seen. Reticulocytosis is common and seems to occur *pari passu* with the normoblastosis.

Our patient, although blood smears were made on numerous occasions, exhibited no normoblasts and no immature white blood cells. On admission, there was no reticulocytosis. Subsequently, a reticulocytosis (6%) developed. The evaluation of this finding is extremely difficult in view of these facts: (*a*) At the time, he had been heavily transfused and his peripheral blood was diluted with transfused blood. (*b*) He was receiving vitamin B_{12} on the assumption that he might have, in view of the bone marrow findings, a pernicious anemia. The relative lack of reticulocytes is even more remarkable in view of the marked hemolysis exhibited by the patient.

The classic bone marrow of myeloid metaplasia shows considerable fibrous replacement with areas of hyperplasia, and it has been stated that in the presence of the above hematologic findings the inability to obtain an adequate marrow aspiration should arouse one's suspicions. In our case repeated bone marrow specimens were obtained with no difficulty. There was no evidence of marked fibrous replacement of bone marrow, and the most striking cellular change in the marrow was the presence of numerous megaloblastic forms. This observation was, in fact, so striking that it was the opinion of at least one observer that this represented a case of pernicious anemia. Block and Jacobson [6] state that the most important single examination is that of splenic tissue obtained by puncture. This tissue almost invariably shows myeloid and erythroid metaplasia and represents the most definite diagnostic measure. No splenic puncture was performed in our case.

The clinical history in these patients is by no means diagnostic. The duration of the symptoms may be anywhere from two weeks, as in our case, to years. The history is compatible with that of any generalized wasting disease, entailing the symptoms of progressive weakness, dyspnea, palpitation, nausea, and quite frequently minimal jaundice. The presenting complaint of some of these patients is a mass or pain in the left upper abdominal quadrant as a result of a large, congested spleen. Of the seven cases reported by Thompson and Illyne,[2b] six had the presenting symptoms of bleeding tendencies. Our patient had noticed no bleeding tendency, and, although he had noticed weakness, nausea, and jaundice, they had been fulminating rather than chronic. On physical examination, the patient is usually pale, is frequently icteric, and frequently shows evidence of ecchymoses. Fever is not at all uncommon. The absence of splenomegaly almost rules out the

5. Jackson and others.[1] Thompson and Illyne.[2b] Block and Jacobson.[2c]

6. Block and Jacobson.[2c] Block, M., and Jacobson, L. O.: Splenic Puncture, J. A. M. A. **142**:641-647 (March 4) 1950.

diagnosis, and hepatomegaly is almost, but not quite, as common as splenomegaly. Peripheral lymphadenopathy is uncommon. This has been so striking that numerous authors have emphasized that anemia in conjunction with splenomegaly in the absence of peripheral lymphadenopathy should call to mind, among other possibilities, the diagnostic possibility of myeloid metaplasia.

In regard to the pathogenesis of the clinical picture and histologic state in our patient, three main possibilities exist.

1. Did this case represent an instance of primary or so-called agnogenic myeloid metaplasia? If this was the situation, did the splenomegaly occurring as part of that disease result in a state of hypersplenism, as manifested by thrombocytopenia, leucopenia, and hemolytic anemia? In such circumstances, was the splenectomy actually contraindicated?

2. This patient's bone marrow, although not aplastic, showed evidence of some arrest at the megaloblastic level. Did this bone marrow arrest result in a secondary myeloid metaplasia, as has frequently been reported secondary to replacement of bone marrow by malignant growth, fibrous tissue, etc.?

3. This possibility is probably the best: namely, that the patient had acquired hemolytic anemia with a secondary myeloid metaplasia.

CONCLUSIONS

In reviewing the case reports covered in the literature and the record of the present case, it strikes us that the diagnosis of agnogenic myeloid metaplasia is rarely, if ever, tenable. At best, it is a misnomer. The myeloid metaplasia can almost invariably be accounted for on the basis of some other disease that interferes with the production of blood, and as such perhaps the term agnogenic could be applied to the primary disease but not to the resultant condition in the spleen and liver. If this is true, the treatment of these patients would depend, not on the finding of myeloid metaplasia of the spleen, but on the nature of the primary disease. Although it has been emphasized frequently in the literature that splenectomy or irradiation of the spleen is contraindicated in myeloid metaplasia, this patient has done remarkably well after the splenectomy. He has continued to manufacture blood and at this time is strong and vigorous, and has a normal peripheral blood picture. A contraindication to splenectomy obviously would be a failure to demonstrate any other capacity of the patient to produce blood. In cases of malignant growth metastatic to bone and of idiopathic osteosclerosis with secondary myeloid metaplasia, splenectomy could well be catastrophic. However, in cases such as the present one, in which the myeloid metaplasia was secondary to a hemolytic process and in which the patient had good resources for hematopoiesis, the primary disease should be treated as it would be if there was no myeloid metaplasia. It is realized, of course, that one case provides a flimsy basis for any generalities on the treatment of the disease. It is hoped, however, that other authors will report their observations in similar cases.

SUMMARY

A report of a case of myeloid metaplasia of the spleen in conjunction with severe acute hemolytic anemia is presented. The features of classic myeloid metaplasia are described and compared with the features presented in the case reported. The theoretical pathogenic possibilities are enumerated, and the value of and contraindications to splenectomy are discussed.

PRIMARY CARCINOMA OF THE LIVER

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FOURTEEN cases of primary carcinoma of the liver have been observed among 797 consecutive necropsies at Kennedy Veterans Administration Hospital since 1946. This incidence (1.76%) stands in striking contrast to the 0.26% calculated average for Americans.[1] Only in the Asiatic and African races have similar incidences been consistently observed, as indicated by the figures of 1.87%[2] reported from Formosa, 1.3% from Java,[3] and 1.2% among the Bantu tribes of South Africa.[3] This unusual incidence has prompted us to review the clinicopathological features of our cases.

All our patients were men, and any analysis of incidence rates must take into consideration both the predominantly male population peculiar to a veterans' hospital and the known predilection of the disease for males. Table 1 illustrates this sex difference in various series. Assuming that the sex ratio is roughly 7:1 in favor of males, an incidence of 1.0% would be expected if our hospital census were composed equally of both sexes. This would still be almost five times the frequency for the United States. It is of interest to compare our figure with that from the Veterans Administration Hospital, Hines, Ill., an institution with a preponderance of male patients similar to our own, where the incidence of 0.629% exists.[4]

All our patients were of American birth and resided for the greater part of their lives in the states of Arkansas, Alabama, Mississippi, or Tennessee. Six, or 42.8%, of the patients were Negroes. Since Negroes comprise approximately 16%

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1. Rosenberg, D. M. L., and Ochsner, A.: Primary Carcinoma of the Liver, Surgery **24**:1036 (Dec.) 1948.

2. Usuda, H., and Uchida, K., cited by Rosenberg and Ochsner.[1]

3. Berman, C., cited by Rosenberg and Ochsner.[1]

4. McNamara, W. L.; Benner, W. H., and Baker, L. A.: Primary Carcinoma of the Liver, Am. J. Surg. **80**:545 (Nov.) 1950.

of the total hospital population, this figure possibly indicates some racial susceptibility. Rosenberg and Ochsner noted a similar racial distribution in patients from the same general locale.[1]

Two of our patients were in the fourth, 11 in the sixth, and 1 in the seventh decade of life. The selective age distribution of veterans precludes comparison with other series.

The role of various suggested etiological factors was not clear cut. A definitely deficient diet was present in only one case; however, in only two was the diet known to have been adequate. Clinically recognizable deficiency states were not seen in any of the patients. Likewise, the importance of alcoholism was difficult to ascertain. Three patients gave histories of excessive alcohol consumption, and cirrhosis was present in all of these. Four of the six patients who denied alcoholism showed cirrhosis. A history of antecedent jaundice or hepatitis was not present in the 13 patients from whom history was obtainable. Trauma or carcinogenic agents could not be incriminated in any of the cases. The importance of hereditary and constitutional factors was indeterminable. The following points were noted in this regard: The brother of one patient was said to have died of "cancer of the liver," but this could not be confirmed. Another patient gave a history of death

TABLE 1.—*Sex Difference in Primary Carcinoma of the Liver in Various Series**

	Spatt & Grayzel	Wilbur et al.	Loesch	Gustafson	Greene
Males, %	65	86	86	85	86
Females, %	35	14	14	15	14

* Reprinted by permission (Spatt and Grayzel [5a]).

of his father and sister due to cancer, and, in addition, a brother died of cirrhosis. The mother and father of still another patient both died of cancer. One patient had had a block dissection of the neck and local excision of a facial skin cancer four years previously.

CLINICAL FEATURES

Opinion varies regarding the existence of a recognizable clinical picture of primary carcinoma of the liver. Certain authors [5] suggest that the clinical features are nonspecific and claim that it is seldom possible to arrive at a correct diagnosis. Others [6] feel that there is a characteristic rapid sequence of events which, though not pathognomonic, is highly suggestive of the correct diagnosis. Primary cancer of the liver was the clinical diagnosis in nine, or 64%, of our cases prior to biopsy or death.

Table 5 indicates that the duration of illness was usually brief. Even the patient listed as surviving 56 weeks may have had symptoms of hepatoma for

5. (*a*) Spatt, S. D., and Grayzel, D. M.: Primary Carcinoma of the Liver, Am. J. Med. **5**:570 (Oct.) 1948. (*b*) Hoyne, R. M., and Kernohan, J. W.: Primary Carcinoma of the Liver, Arch. Int. Med. **79**:532 (May) 1947. (*c*) Holley, H. L., and Gray, P.: Primary Carcinoma of the Liver, Am. J. Med. **5**:561 (Oct.) 1948.

6. Rosenberg and Ochsner.[1] Strong, G. F.; Pitts, H. H., and McPhee, J. G.: Primary Carcinoma of the Liver: 25-Year Study, Ann. Int. Med. **30**:791 (April) 1949. Warvi, W. N.: Primary Neoplasms of the Liver, Arch. Path. **37**:367 (June) 1944.

a much shorter period. Though he gave a history of vague gastrointestinal and constitutional symptoms beginning 56 weeks before death, he subsequently remained asymptomatic for seven months and then died after an illness of seven weeks.

In our experience signs of progressive portal hypertension, the nodular enlargement of the liver, often visibly "growing" from day to day, and the ensuing

TABLE 2.—*Frequency of Major Symptoms and Signs*

Symptom or Sign	%
Hepatomegaly	93
Abdominal pain	93
Weight loss	86
Fever	86
Portal hypertension	71
Ascites	57
Pedal edema	50
Dilated abdominal veins	29
Protruding hemorrhoids	29
Splenomegaly	21
Spider nevi	36
Jaundice	36
Gastrointestinal hemorrhage	29

TABLE 3.—*Laboratory Data*

	Normal Levels	Number Tested	Number Abnormal	Range
Red blood cells	Above 4,000,000	14	7	2,700,000-3,900,000
Eosinophil count, %	Below 5	14	2 Eosinophilia	7-8
Intestinal parasites	.....	10	1 *	.....
Serologic reactions for syphilis	.....	13	3	.....
Total protein, gm./100 cc.	6-8	12	1 Elevated	9.2
	.....	12	3 Decreased	5.0-5.3
Albumin, gm./100 cc.	3.5-4.5	12	10 Decreased	1.8-3.3
Globulin, gm./100 cc.	2.0-3.6	12	7 Elevated	3.8-5.9
Sulfobromophthalein retention, %	0-10	11	10 Increased	15-60
Cephalin flocculation	0 to 2+	11	4	3 to 4+
Thymol turbidity, cc.	0-1.4	11	4	2.4-3.6
Alkaline phosphatase †	0-15	11	0	.....
Prothrombin time, % of normal	Above 70	9	5 Hypoprothrombinemia	38-59
Bilirubin, mg./100 cc.	0.2-0.8	12	9 Hyperbilirubinemia	1.25-12.3

* Endamoeba histolytica.
† King-Armstrong units.

cachexia were sufficient to warrant serious consideration of primary neoplasm of the liver as a diagnosis. Spider angiomas, jaundice, right upper abdominal quadrant and right chest pain, and impairment of liver function were variably present and served to strengthen the clinical impression. Fever, nausea, vomiting, gastrointestinal hemorrhage, splenomegaly, weakness, and dyspnea were often present but of no great aid in diagnosis. Terminally, the picture was usually that of coma and, frequently, cholemia. Table 2 summarizes the frequency of major signs and symptoms.

LABORATORY FINDINGS

The results of laboratory studies are summarized in Table 3. Results of other examinations included normal serum amylase levels in four patients and abnormally low cholesterol esters in two of four patients in whom the cholesterol-cholesterol ester ratio was determined. Liver function tests were performed on 12 patients and all showed abnormalities on one or more of these tests. Sulfobromophthalein (bromsulphalein®) sodium retention and inversion of the albumin-globulin ratio were the commonest changes. Though lacking diagnostic specificity, these various examinations afforded valuable corroborative evidence of serious, often progressive, hepatic dysfunction.

ROENTGENOGRAPHIC FINDINGS

Hepatomegaly was demonstrated on roentgenograms in six patients. Ascites and flattening or elevation of the right leaf of the diaphragm were noted in four. Miscellaneous findings included splenomegaly in two and the following in one instance each: nonvisualization of the gall bladder, displacement of the duodenum, displacement of the right kidney, focal atelectasis at the base of the right lung, osteoporosis of the dorsal and lumbar portions of the spine, and metastatic nodules in the lung. Esophageal varices were also demonstrable in one patient who, incidentally, had severe hematemesis just prior to death. One patient had a benign gastric ulcer which healed after ulcer therapy.

PARACENTESIS AND BIOPSY

Ascitic fluid was examined for tumor cells in six patients, and none were found. In eight cases liver biopsies were performed as a diagnostic measure. In five cases the tissue was obtained by needle aspiration, and in the remaining three small blocks of tissue were surgically excised at the time of exploratory laparotomy. In all instances a histologic diagnosis of carcinoma was established. In four of the eight biopsy specimens it was possible to identify the neoplasm as being either conclusively or probably a primary tumor of the liver. In one case a clinically misleading report of "metastatic carcinoma" was made.

PATHOLOGIC ASPECTS

The pathologic studies on this series of 14 cases of primary epithelial tumors of the liver, although agreeing generally with the features previously presented in the literature, revealed a number of unusual findings. The most striking features were in the distribution of histologic types, the frequency of metastases, and the lack of relationship between the degree of histologic malignancy and the duration of life.

Hepatomas are said to far outnumber cholangiomas, the latter comprising less than 20% of primary liver tumors. Mixed tumors, that is, tumors composed of both liver cells and bile-ductule cells, are considered to be the commonest variety. Our observations revealed 2 of the 14 growths to be cholangiomas, 7 of the 14 to be hepatomas, and 5 of the 14 to be mixed tumors, with bile-duct cells predominating in 3 cases and hepatic cells predominating in the remaining 3.

It is believed that cholangiohepatomas and/or hepatocholangiomas are commoner than is generally indicated in the literature. The microscopic differentiation

between hepatomas and cholangiomas, while readily apparent in most instances, is, in a considerable percentage of cases, not clearly definable and not of clinical importance. In most of the mixed tumors the distribution of the two cell types is well mixed and haphazard. In many instances the transition from one cell type to another is vague and indefinite. The opinions regarding the specificity of bile-duct cells and liver cells differ. Lucké [7] has clearly presented the genetic relationship relationship between the two cells and has demonstrated the origination of liver cells from bile-duct epithelium. It seems highly probable that in tumors of the liver this same transition and combination of liver and bile-duct cells not infrequently occur and explain the origination of mixed tumors.

Gross Features.—In all but a single case, the livers were markedly enlarged. The average weight was 3,653 gm., with a range of 1,320 to 6,950 gm. In two cases the neoplasms were large and solitary; in the remaining 12 the liver tissue was extensively replaced by numerous, various-sized nodules. It cannot be ascertained whether the multiple nodularity was the result of intrahepatic metastasis or arose as multicentric foci. In one instance the incidental discovery at necropsy of an

TABLE 4.—*Frequency of Sites of Metastases in Twelve Patients*

Organ	%
Regional lymph nodes	67
Lungs	67
Gall bladder	25
Pancreas (head)	17
Lumbar portion of spine *	8
Peritoneal seeding	8
Spleen	8
Adrenal gland, left	8

* Not examined in all cases.

early, multifocal hepatoma lends strength to Willis' [8] concept that genuine multiple origin does occur in many cases and that not all multiple nodules are the result of intrahepatic spread from a solitary tumor.

Generally, the liver tumors in this series were described as soft, with colors varying from grayish-white to yellowish-tan. The softness is in sharp contrast to the consistency of most carcinomas, which are usually firm to hard and gritty. This feature may represent a helpful point in distinguishing primary neoplastic nodules in a liver from metastatic ones.

The well-known relationship to cirrhosis was evident by the occurrence of portal (Laennec's) cirrhosis in 57% of the cases. All the five cholangiohepatomas and hepatocholangiomas arose in cirrhotic livers; three of the seven cases of hepatoma were related to cirrhosis. It is interesting to note that in neither of the two cases of cholangioma was there gross or microscopic evidence of portal cirrhosis.

Splenomegaly occurred in 9 of the 14 cases, the average weight of the spleen being 502 gm. as determined at necropsy.

7. Lucké, B.: The Pathology of Fatal Epidemic Hepatitis, Am. J. Path. **20**:471 (May) 1944.
8. Willis, R. A.: Pathology of Tumors, St. Louis, C. V. Mosby Company, 1948.

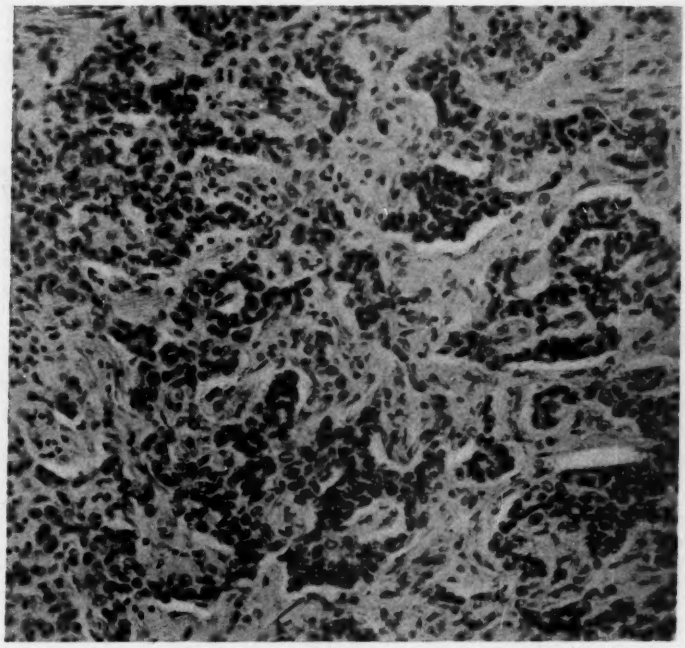

Fig. 1 (Case 2).—Photomicrograph of cholangioma, showing abundant fibrous stroma and occasional duct-like structures; × 100.

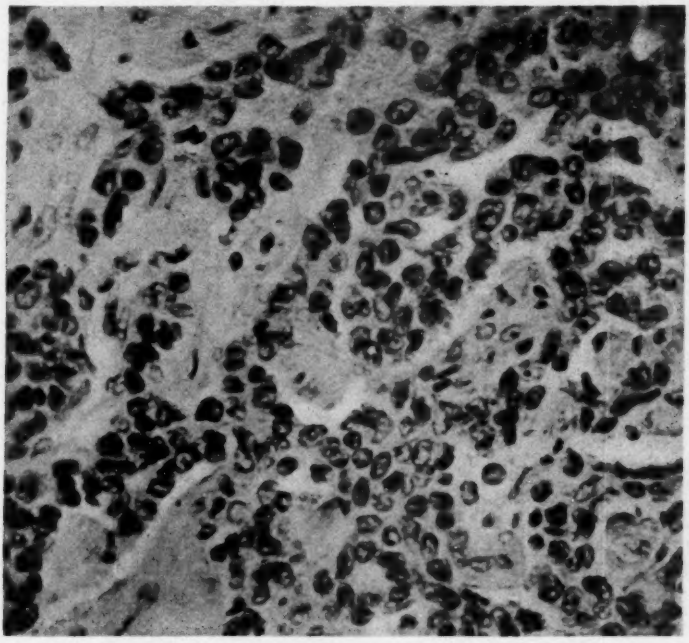

Fig. 2 (Case 2).—Photomicrograph of cholangioma, showing duct-like structures and uniformity of cells; × 200.

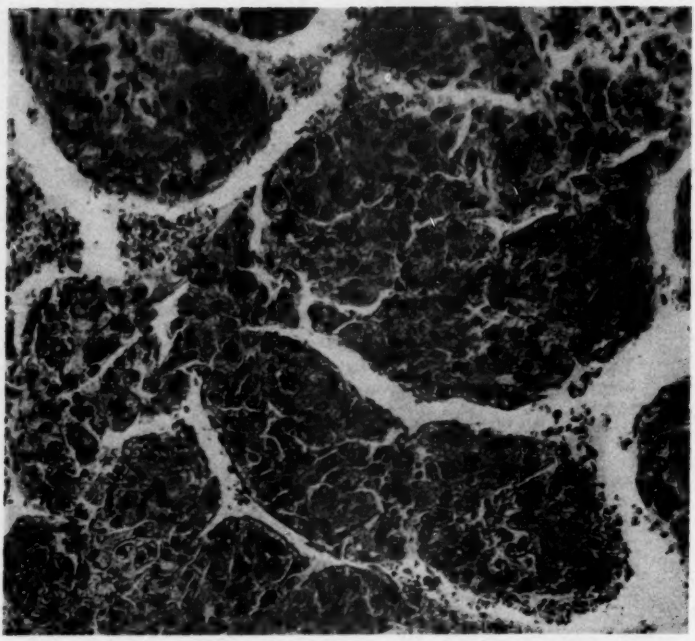

Fig. 3 (Case 11).—Photomicrograph of hepatoma, showing broad, cellular trabeculae, i. e., exaggerated liver cords, and intervening vascular sinusoids; × 100.

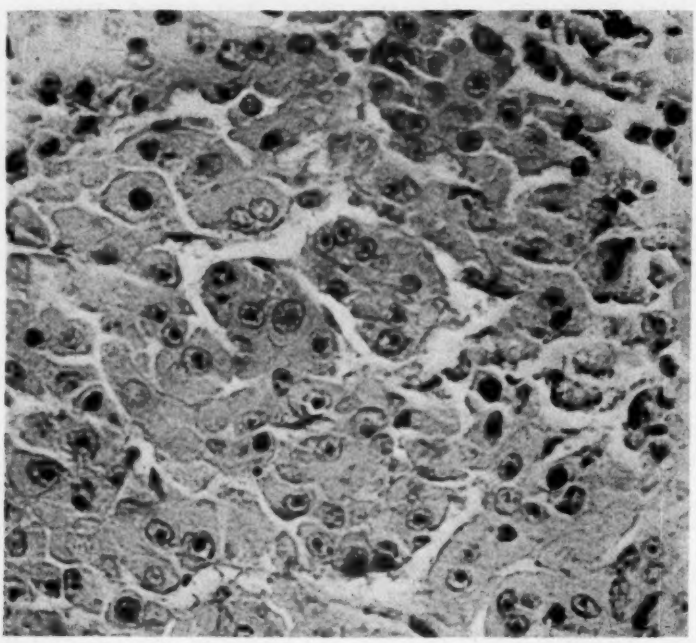

Fig. 4 (Case 10).—Photomicrograph of hepatoma, showing liver-like cords and cells. The cells are well differentiated with little pleomorphism; × 200.

The high incidence of metastatic phenomena in this series differs from that usually presented in the literature. Twelve of the 14 cases revealed extrahepatic metastases (Table 4). In the two cases in which no metastases occurred outside the liver, there was, however, multiple intrahepatic spread.

The frequency with which there was evidence of tumor invasion of endothelium-lined spaces (blood vessels and lymphatics) readily explains the high incidence of metastases to regional lymph nodes and lungs.

Histologic Features.—The cholangiomas were characterized by an abundant fibrous stroma, in sharp contrast to the hepatomas, in which stroma was scant. The

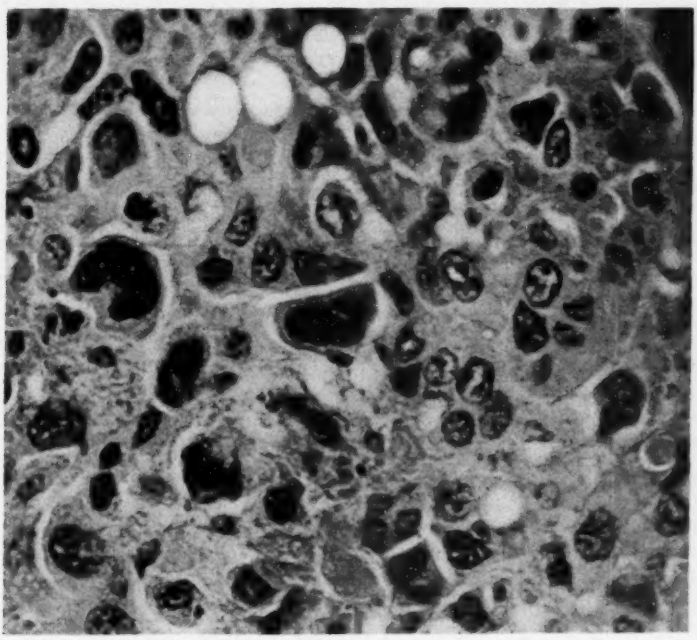

Fig. 5 (Case 13).—Photomicrograph of hepatoma, showing marked cellular pleomorphism, with loss of cord-like structures; × 200.

latter tumors showed marked tendencies for the neoplastic cells to proliferate in thick, budding trabeculae to form exaggerated liver cords and sinusoids. The mixed tumors, in general, mimicked the cellular trabeculae of pure hepatomas but contained varying numbers of duct-like acini and cells recognizable as being derived from the biliary ductules. Although only two examples of pure cholangioma were available for histologic examination, they showed little pleomorphism as compared with the hepatomas. The latter possessed cells which in a few cases were well differentiated, regular in size and shape, and with liver-cell-like features. In most of the hepatomas there was great variation in cell configuration, with giant nuclear and multinucleated forms being not uncommon.

The relative degree of malignant tendency, as manifested by number of mitoses and cellular pleomorphism, showed no correlation with the rapidity of the clinical course. Table 5 illustrates these findings.

TREATMENT

The extreme pessimism existing in the literature regarding treatment of primary carcinoma of the liver is unfortunate. On the surface, our experience leaves no room for optimism. Surgical exploration was done in three cases, and they were found to be inoperable. However, in two cases in which exploration was not done solitary hepatic nodules were observed at necropsy. It is conjectural whether the lesions could have been excised in these patients even if metastasis had not yet taken place, but the occurrence of solitary hepatic nodules in 14% of our cases would seem to warrant early laparotomy whenever possible, for otherwise

TABLE 5.—*Diagnosis, Relative Degree of Malignant Tendency, and Duration After Onset in Fourteen Patients with Primary Carcinoma of Liver*

Case No.	Diagnosis	Degree of Cellular Pleomorphism	Relative Number of Mitoses	Duration of Life, Weeks
1	Cholangioma	Slight	Very numerous	4
2	Cholangioma	Slight	Numerous	31
3	Cholangiohepatoma	Moderate	Occasional	28
4	Cholangiohepatoma	Marked	Occasional	28
5	Hepatocholangioma	Slight	Occasional	6
6	Hepatocholangioma	Marked	Occasional	22
7	Hepatocholangioma	Moderate	Occasional	7
8	Hepatoma	Moderate	Few	11
9	Hepatoma	Marked	Few	3
10	Hepatoma	None	Occasional	..
11	Hepatoma	Marked	Occasional	8
12	Hepatoma	Very marked	Very numerous	56
13	Hepatoma	Marked	Very numerous	8
14	Hepatoma	Marked	Very numerous	22

the outcome is invariably fatal. In cases in which successful extirpation has been performed, remarkable results have been obtained. For example, 12 of 29 patients were known to be alive and well for periods up to five years after resection of hepatomas in the series reported on by Wallace.[9]

CONCLUSIONS

The incidence of primary carcinoma of the liver at this institution is 1.76% of all necropsies, a figure which is unusually high for this country.

A correct clinical diagnosis was made in 64% of the cases prior to biopsy or death.

Metastases were observed in 86% of the cases at necropsy.

There was no significant correlation between the survival time and the histologic appearance of the tumor.

More frequent surgical exploration would seem warranted in the belief that successful resection of solitary liver tumors could be occasionally accomplished.

Box 243, Wytheville, Va. (Dr. Schupbach).

9. Wallace, R. H.: Resection of the Liver for Hepatoma, Arch. Surg. **43**:14 (July) 1941.

SYNDROME OF JOINT AND CARTILAGINOUS PATHOLOGIC CHANGES WITH DESTRUCTIVE IRIDOCYCLITIS

Comparison with Described Concurrent Eye and Joint Diseases

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ALL OPHTHALMOLOGISTS of experience have seen rheumatoid arthritis associated with destructive iridocyclitis and perhaps blindness. These patients ordinarily show severe ankylosis in many joints, and frequently they are more or less helpless because they are frozen in one position. There are a number of other joint diseases associated with iridocyclitis as described below. The patient who is the subject of this report, however, presented a concurrent destructive iridocyclitis, atrophy or deformity of body cartilages, and multiple joint dislocations, without any destruction of either bone or joint surface. This syndrome was not familiar to me, and I have been unable to find anything just like it described in the literature.

REPORT OF CASE

Mrs. H. E., aged 61, when seen first in May, 1949, was complaining of rheumatism and blindness. She had been considered well until January, 1947, when a sequence of symptoms developed which was initiated by a feeling of warmth on the medial aspect of the knees. This was followed by difficulty in assuming the erect position after kneeling; soon pain and swelling were noted in the knees. This process of pain, swelling, and limitation of motion progressed to involve the shoulders, wrists, ankles, and many of the small joints of the fingers and toes, as well as the knees.

She was hospitalized in March and again in October, 1947, when she was given fever therapy and certain antibiotics. The diagnosis on discharge was given as chronic rheumatoid arthritis, chronic cervicitis, and secondary anemia. She complained a little of her eyes during this stay, and I saw her briefly one day. The only objective finding, on bedside examination, was congestion of the bulbar conjunctiva. In the light of what followed, this was probably due to scleritis.

In the interim between her hospitalization in 1947 and my examination in May, 1949, the joint pain and swelling practically disappeared, and she was able to walk on crutches. Many of the joints of the hands and feet remained deformed, but the larger joints seemed about normal. It was said that at one time both external ears swelled like balloons and drained fluid. The patient's voice changed from one having the quality of a high-pitched soprano to one having a masculine character. Her vision began to fail in the early part of 1948, a few months after she left the hospital, and this loss progressed steadily to blindness.

The patient's past history revealed only that she had had mastitis and pneumonia 30 years previously. With the latter alopecia developed. She had had no other illnesses and no previous rheumatism. However, she claimed an unusual degree of suppleness of her joints, which she declared exceeded that of her young daughters. When questioned, she did not feel that this suppleness was abnormal in degree.

The marital history disclosed that her husband and seven of her eight children were living and well.

Examination on the first visit (May 27, 1949) showed a cheery comfortable patient who sat in a chair like an invalid. She spoke in an unusually deep voice for a woman. Tension of the

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eyes was low on tactile examination, being lower in the right eye than in the left, and both eyes were pale, save for one or two rather prominent veins crossing the sclera at the outer canthus. The extraocular movements seemed normal. The corneas were clear and the anterior chambers shallow (the right more than the left); the irides bulged forward as in iris bombé and were atrophic, grade II to III. The pupillary margins were adherent to the lens capsule, and both lenses were cataractous, grade III. Vision was limited to light perception, being somewhat better in the left eye than in the right. The pupils were stationary, probably from adhesions. There were many pigment granules on the lens capsule in the pupillary area.

On examining the ears (Fig. 1), it was noted that both pinnas were thickened, deformed and compressed. The ear canals were clean; the right eardrum membrane was pale and intact, but the left was red, grade I. Hearing was noticeably impaired. Subsequently an audiogram indicated perception deafness.

There was an atrophy of the cartilages of the nose (the septal, the alar, and upper lateral cartilages) (Fig. 1), with a resultant saddle of the lower bridge and a drooping and softening

Fig. 1.—Profile view showing deformity of nose and ears resulting from involvement of alar, septal, and upper lateral cartilages of nose and concha of pinnas. Nasal cartilages seemed to have disappeared entirely, whereas cartilages of the ears were left greatly thickened and deformed.

of the tip. On anterior rhinoscopy the septal cartilage seemed to be entirely absent and the septum very soft and mobile. The nasal mucous membranes appeared normal; the breathing spaces were ample. The throat was not remarkable. The mandible moved freely, but there seemed to be some discomfort in the mandibular joint when the jaw was opened widely. On palpation the larynx seemed to be somewhat flattened in an anteroposterior direction.

Examination of the thorax showed the lower two-thirds of the sternum to be abnormally mobile at the manubrial joint. The rib cartilages all seemed to be soft, and the sternum retracted on inspiration. The left sternoclavicular joint could be dislocated at will by the patient on manipulation of the shoulder. The lower end of the ulna (Fig. 2) in both arms was prominent and obviously dislocated. The phalanges were dislocated ventrally from the corresponding metacarpal bones, resulting in shortening of many fingers. Similar deformities were present in the toes. Superficial inspection did not reveal any deformity of the shoulders, elbows, knees, or

pelvic joints. Atrophy of the skin, rather marked for a patient of this age, was present. The alopecia, which had begun 30 years ago, was evident.

It was felt that the patient had (1) a quiescent plastic iridocyclitis and bilateral degenerative cataracts, with other degenerations probable within the eyes, (2) quiescent polyarthritis with abnormal mobility of the joints and multiple dislocations, and (3) an affection of the cartilages resulting in atrophy and degeneration.

Because there was light perception in both eyes, cataract extraction, though fraught with hazards, was thought to be worthy of consideration.

The patient was studied further on July 21, 1949, when she was brought to the office and examination made with a corneal microscope. On the right, this revealed some punctate opacities in the superficial layers of the cornea over the medial pupillary area, but the remainder of the cornea was clear. The iris was atrophic, grade III. There seemed to be posterior adhesions to the lens over much of the surface of the latter. Pigment was present on the

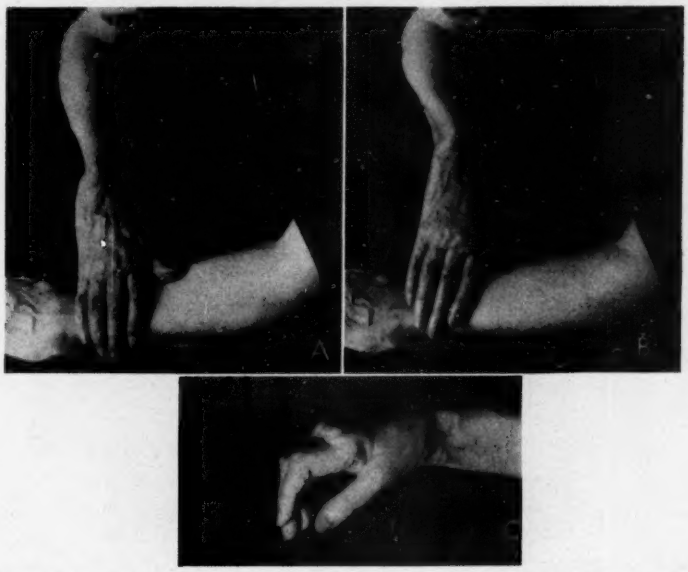

Fig. 2.—Deformity of hand and wrist resulting from multiple dislocations due to extreme laxness of joint ligaments. *A*, ulna at rest. *B*, ulna lifted. *C*, dislocation of proximal phalanges toward palmar surface of hand. Neither carpals nor phalanges showed any enlargement or anklyosis either clinically or roentgenologically.

anterior lens capsule, and numerous blood vessels were seen in the iris, many of them coming over the edge of the pupillary margin from behind to the anterior surface. The lens was cataractous, grade IV, and the anterior chamber was almost empty. On the left, the cornea showed quite a number of old keratic precipitates on the posterior surface and fine lace-like opacities on the anterior surface but otherwise was reasonably clear. The anterior chamber was about one-half normal depth. There was a moderate degree of iris bombé; the iris was similar to that on the right except that the atrophy and vascularity were not as marked in the left eye. There was no pupillary reaction, and the lens was cataractous, grade IV. Intraocular tension, measured with both the Schiøtz and the McLean tonometers, was 0 in the right eye and 13 mm. in the left.

Subsequently, the patient was photographed (Figs. 1 and 2); roentgenograms (Fig. 3) of many of the joints were taken and blood studies instituted. On Aug. 24, 1949, the sedimentation

rate was 13 mm. in one hour; red blood cells numbered 3,980,000, with 85% hemoglobin; there were 7,650 leucocytes and a normal differential count, except for 11% eosinophils (49% polymorphonuclear cells, 35% lymphocytes, 1% basophils, 4% monocytes, and 11% eosinophils). The urine was normal; there was no alkaptonuria. The blood phosphorus was 4.06 mg. and the blood calcium 10.75 mg. per 100 cc.

On Feb. 15, 1950, a preliminary iridectomy was done on the left eye. It was deemed wise to see how the eye would tolerate surgical measures before attempting to free and extract the lens. The pathologist reported that there was no significant inflammatory or neoplastic change in the small piece of iris received for examination. It did, however, contain atrophic changes and thickening and hyalinization of the walls of the small vessels. The postoperative course was quite uneventful, and, when the patient was seen on March 7, 1950, the anterior chamber of the left eye was shallow; there was some congestion of the iris but not appreciably more than before the operation. The tension in the left eye on tactile examination was low but still somewhat higher than in the right; when intraocular tension was measured on the McLean tonometer it was 0 in the right eye and 6 mm. in the left.

Fig. 3.—Roentgenographic views of one hand, showing dislocations. There is extensive osteoporosis, but otherwise the bony contours all appear normal, with the exception of the lower end of the ulna. Interphalangeal spaces appear somewhat narrowed, as though cartilages were thinned or absent.

About April 1, 1950, began her first noteworthy exacerbation since the remission of symptoms after her illness three years earlier; this exacerbation consisted in moderate swelling and pain in the joints; the eyes remained quiet. Laboratory data were procured when the patient was hospitalized for several days in May, 1950. The urinalysis gave normal results, showing only 0 to 8 white cells and 0 to 1 red cells. The icterus index was 7 units; erythrocytes numbered 4,100,000; the hemoglobin concentration was 12 gm. (84%). There were 6,900 leucocytes; a differential count showed 2% basophils, 3% eosinophils, 1% stab cells, 54% segmented polymorphonuclear cells, 37% lymphocytes, and 3% monocytes. The sedimentation rate was 53 mm. in an hour. The cephalin-cholesterol flocculation was 3+ in 24 hours and 4+ in 48 hours. Plasma albumin was 4.28 gm. and plasma globulin 2.40 gm. per 100 cc. Bence Jones protein was not found in the urine. A second sedimentation rate, determined one week following the first, was 44.5 mm. in an hour. Tests for Brucella organisms and a blood Wassermann test made elsewhere were reported as having negative results.

A specimen for biopsy was taken from the cartilage of one of the external ears. This was studied for amyloid by three different pathologists, none of whom was very certain of what it showed. Dr. Shields Warren,[1] of Boston, stated that the amyloid stain was "slightly positive" but did not feel that it was specific or significant.

Roentgenograms (Fig. 3) were made of the pelvis, lumbar portion of the spine, left shoulder, right knee, hand, and wrist. All the bony structures showed marked osteoporosis without selection of any portion of the bones. There were marked thinning of the bony cortex in all bones and slight narrowing of the hip joint spaces, but the bony contours were normal. The sacroiliac joints were normal, and the pelvis was normal except for osteoporosis, as were the left shoulder joint and knee. There was considerable fluid within the knee joint and the suprapatellar bursa, which was markedly distended. No significant narrowing of the joint spaces (wrists, knees, and hips) was noted, with the possible exception of the phalanges, but there was complete anterior dislocation of the metacarpophalangeal joints, save for the thumb. The ulna was dislocated posteriorly, with atrophy and possibly some destruction at the distal end. One small fragment was loose in the soft tissues. The roentgenologist concluded that many of the findings were similar to rheumatoid arthritis but differed in that there was no marked abnormality of bone, other than osteoporosis, no joint destruction, and no ankylosis. There were severe deformities,

Fig. 4.—Comparison of hip joints in the patient here reported on (left) and a patient having usual rheumatoid arthritis with complicating iridocyclitis (right). Patient here reported on (left) shows no joint destruction and has lost the vision of both eyes. The joint in the right roentgenogram shows extensive destruction of the acetabulum and head of the femur, with lipping of the joint and ankylosis; this patient has lost the vision in one eye. The involvement and destruction of the ocular structures are more extensive in the patient here reported on than in the other. Both are bedridden, the present patient because of dislocations and the other because of extensive ankylosis. (There is a fracture just below the trochanter in the roentgenogram on the right which resulted from manipulation incidental to cystoscopy.)

but these seemed to be due entirely to dislocation and not to bony enlargement or other abnormality (Fig. 4).

The exacerbation gradually subsided, and the patient returned to her previous state in July, 1950. The left cataractous lens was extracted Nov. 29, 1950. The adhesions between the iris and the lens separated rather readily, and the lens, which was found to be almost spherical, was extracted intracapsularly without a great deal of difficulty. Upon removing the lens, it was observed that there was a white, dense, retrolental membrane stretching across the anterior portion of the vitreous chamber. The corneal flap was lifted and an incision made through

1. When Dr. Warren reviewed the history and biopsy specimen, he wondered whether syphilis was present and thought the changes in the cartilage were compatible with that disease, although the history was somewhat against it. His other suggestion was atypical rheumatoid arthritis.

the center of this membrane. Instead of normal clear vitreous behind it, a brownish-yellow fluid appeared. No vitreous was seen. The postoperative course was uneventful, the eye healing with little reaction. When the bandage was removed, the patient complained rather bitterly of strong light, but, for all practical purposes, the eye remains entirely blind. Apparently the vitreous, retina, and ciliary body had been irreparably damaged by the disease process. The eye remans soft. This would ordinarily lead one to assume that there was a dearth of aqueous formation. However, an air bubble left in the anterior chamber disappeared at about the same rate as in the ordinary case of cataract extraction. Perhaps the eye is exceedingly soft, not because of a lack of aqueous production, but because of excessively rapid drainage of aqueous.

CIRCULATION OF THE EYE AND PRODUCTION OF AQUEOUS HUMOR

Numerous general diseases, including those of joints, gain access to the eye through the ciliary circulation, and it might be well to review this anatomy briefly. The eye contains three circulations, two of blood and one of intraocular fluid. The blood circulations are the retinal and the ciliary. The ciliary circulation is made up of an anastomotic network between the long and short ciliary arteries which pierce the sclera posteriorly and the seven anterior ciliary arteries which penetrate the sclera anteriorly. This anastomotic network is so rich in blood supply that it is a veritable mat of vessels and is similar to erectile tissue. It supplies the outer retinal layers and the choroid, ciliary body, and iris, the latter three constituting the uveal tract. It is the ciliary circulation in the ciliary body which produces the aqueous or intraocular fluid.

The aqueous circulates within the eye, serving the metabolic needs of the cornea and lens, possibly the vitreous body and probably the surfaces of the iris and retina, especially the endothelium. The aqueous is produced by a combination of filtration and complex processes of secretion by the stroma of the ciliary body and the endothelium covering it. The permeability of the capillaries is not as great in the ciliary circulation as elsewhere in the body. Water and electrolytes pass readily, but proteins do not. The pressure relations among the capillaries, intraocular fluid, and draining vein systems are most important for the metabolism of the eye and the function of its parts. Any disturbance in these pressure relationships or in the amount or quality of the aqueous produced has profound effects upon the eye.

The ciliary circulation in the choroid, ciliary body, and iris carries a large volume of blood through a fine capillary network and is, therefore, subject to numerous blood-borne diseases. Metastatic infections lodge there—suppurative, granulomatous (tuberculosis, syphilis, leprosy), viral, and fungous. It is subject to allergic and toxic inflammations. It shares in the effects of febrile diseases, such as exanthems, acute intestinal diseases (typhoid, cholera, dysentery), blood infections (malaria), respiratory infections, meningitis, and disturbances of the salivary glands (mumps). Inflammations of the uveal tract are often associated with skin diseases, as well as with metabolic or endocrine disturbances, such as rheumatism, gout, diabetes, and nephritis. All these and many more blood-borne disturbances come filtering through the network of the ciliary circulation. As a consequence, the uveal tract shares profoundly in a host of general systemic diseases.

One can readily understand what happens when a destructive agent, circulating over a period of time through the network, damages the capillary walls, making them more or less permeable or perhaps closing them entirely. Structures within the eye are injured by the toxins and by lack of nutrition or other disturbances of

metabolism. The production of aqueous is decreased, and its osmotic and balanced hydrostatic pressures are altered; the lens degenerates and becomes cataractous. The iris first becomes inflamed and later atrophic. The endothelium is damaged and replaced by the weed cells of the body—the fibroblasts—resulting in adhesions. If the adhesions surround the pupil completely, the exit of the aqueous from the eye is cut off; the iris bulges forward into what is called iris bombé, and secondary glaucoma results. The production of aqueous may finally nearly cease, in which case hypotonia results instead of glaucoma. The intraocular pressure may reach 0; eventually the retina degenerates, and light perception is lost. The iris, ciliary body, and choroid become inflamed, swollen, and infiltrated and finally atrophy.

Iridocyclitis—the process just described—with more or less complete destruction of the function of the eye, occurs in association with certain joint diseases, both the iridocyclitis and the arthritis resulting presumably from the same noxious agent.

Although there is extensive literature on concurrent eye and joint disease,[2] it is somewhat confusing and not entirely clear, and a search failed to reveal any literature on a syndrome involving cartilages outside the joints. Erik Godtfredsen,[3]

TABLE 1.—*Incidence (Percentage) of Eye Symptoms Complicating Joint Diseases*

	Conjunctivitis	Iritis	Sicca Syndrome *
Acute joint diseases			
Rheumatic fever	5-10	4-5	..
Gonorrheal arthritis	10	5	..
Reiter's disease	80	10	..
Uratic arthritis	..	2	..
Chronic joint diseases			
Primary progressive chronic polyarthritis	..	2-5	10
Still's disease	..	20	..
Ankylopoietic spondyloarthritis (Bechterew-Strümpell-Marie)	..	15-50	..

* Keratoconjunctivitis sicca, or Sjögren's disease.
From Godtfredsen.[3]

2. Bentley, N.: Iritis and Iridocyclitis: Review of Past and Present Ideas, J. Michigan M. Soc. **49**:166-173 (Feb.) 1950. Berens, C.; Rothbard, S., and Angevine, D. M.: Cultural Studies on Patients with Uveitis and Other Eye Diseases, Am. J. Ophth. **25**:295-301 (March) 1942. Eggers, H.: Necroscleritis Nodosa Associated with Chronic Rheumatoid Polyarthritis: Report of Case, Arch. Ophth. **23**:501-506 (March) 1940. Harbater, M.: Scleromalacia Perforans: Report of a Case, ibid. **41**:183-187 (Feb.) 1949. Kurnick, N. B.: A Rare Syndrome of Band-Shaped Keratitis and Arthritis, Am. J. Dis. Child. **63**:742-747 (April) 1942. Mann, W. A., and Markson, D. E.: A Case of Recurrent Iritis and Episcleritis on a Rheumatic Basis Treated with ACTH, Am. J. Ophth. **33**:459-461 (March) 1950. Novoa-Recio, F. E.: Importance of X-Rays and Red-Blood-Cell Sedimentation Rate in the Diagnosis and Treatment of Different Forms of Arthritis Complicated with Iritis, Arch. oftal. Buenos Aires, **16**:36 (Jan.) 1941; abstracted, Am. J. Ophth. **25**:761-762 (June) 1942. Recordon, E. G.: Modern Views on the Causation and Treatment of Irido-Cyclitis, M. Press **216**:245-248 (Oct. 2) 1946. Smoleroff, J. W.: Scleral Disease in Rheumatoid Arthritis: Report of Three Cases, in One of Which Both Eyes Were Studied post Mortem, Arch. Ophth. **29**:98-108 (Jan.) 1943. Sorsby, A., and Gormaz, A.: Iritis in the Rheumatic Affections, Brit. M. J. **1**:597-600 (April 20) 1946. Wong, R. T.: Band-Shaped Opacity of the Cornea Associated with Juvenile Atrophic Arthritis: Report of a Case, Arch. Ophth. **26**:21-24 (July) 1941.

3. Godtfredsen, E.: Pathogenesis of Concurrent Eye and Joint Diseases, Brit. J. Ophth. **33**:261-270 (May) 1949.

of Copenhagen, made a study of concurrent eye and joint disease. He classified rheumatic joint diseases complicated by ocular symptoms as indicated in Table 1. He showed further diseases with concurrent symptoms from the eyes, joints, skin, and mucous membranes, as presented in Table 2.

Reiter's syndrome consists of polyarthritis, urethritis, and conjunctivitis. It was especially prevalent after World War II. Still's disease is a chronic polyarthritis of children, especially girls, which leaves iris adhesion. Ankylopoietic spondyloarthritis (Bechterew-Strümpell-Marie) involves the sacroiliac and the spine and is frequently complicated by iritis. The eye symptoms are infrequent in the common joint diseases and frequent in the rarer diseases. The pathogenesis is probably the same for both the eye and the joints and is likely allergotoxic in nature. Phlyctenules, episcleritis, Aschoff nodules in the heart, and rheumatic nodules on the skin are all similar histologically. They show polymorphonuclear neutrophils, small lympho-

TABLE 2.—*Diseases with Concurrent Symptoms from Eyes, Joints, Skin and Mucous Membranes* *

	Eyes	Joints	Skin	Mucous Membranes (Stomatitis, Balanitis)
Virus diseases of obscure etiology				
Reiter's disease	+	+	+	+
Stevens-Johnson syndrome	+	(+)	+	+
Behcet's syndrome	+	(+)	+	+
Foot and mouth disease	+	?	+	+
Acute disseminated erythematous lupus	+	+	+	+
Measles, chickenpox	+	(+)	+	+
Bacterial diseases				
Gonococcal sepsis	+	+	(+)	+
Streptococcal sepsis	(+)	+	+	+
Intoxications				
"Sanocrysin," † arsenicals	+	(+)	+	+
Serum sickness	+	+	+	+

* Plus sign enclosed in parentheses means symptom is less significant.
† Gold sodium thiosulfate.
From Godtfredsen.[3]

cytes, and epithelioid cells, which are sometimes polynuclear. Godtfredsen stated that the blood-aqueous and the blood-synovial barriers are similar and that the ciliary processes of the eye and the synovia of the joints are alike susceptible to streptococci.

Stevens-Johnson syndrome is a form of exudative erythema multiforme with conjunctivitis and stomatitis. Behcet's syndrome involves ulceration of the genitals and mouth, together with uveitis and joint disease.

It has been suggested that this patient's condition may be a form of Ehlers-Danlos syndrome (cutis hyperelastica).[4] It is true that the hyperlaxity and hyperextensibility of the joints might suggest this, but none of the other characteristics

4. Benjamin, B., and Weiner, H.: Syndrome of Cutaneous Fragility and Hyperelasticity and Articular Hyperlaxity, Am. J. Dis. Child. **65**:247-257 (Feb.) 1943. Freeman, J. T.: Ehlers-Danlos Syndrome, ibid. **79**:1049-1056 (June) 1950. Johnson, S., and Falls, H. F.: Ehlers-Danlos Syndrome: A Clinical and Genetic Study, Arch. Dermat. & Syph. **60**:82-105 (July) 1949. Pray, L. G.: Cutis Elastica (Dermatorrhexis, Ehlers-Danlos Syndrome), Am. J. Dis. Child. **75**:702-711 (May) 1948.

is present, such as hyperelasticity, hyperlaxity or friability of the skin with multiple scars, vulnerability and fragility of the blood vessels, or the small cyst-like tumors found in the subcutaneous tissue. Moreover, Ehlers-Danlos syndrome usually occurs in youth, whereas this patient's condition did not have its inception until the end of the sixth decade. In addition, this patient has suffered destructive iridocyclitis with blindness and damage or destruction of certain cartilages, none of which is commonly associated with Ehlers-Danlos syndrome. In my opinion the latter syndrome can be ruled out.

SUMMARY

The case here presented seems to be related to rheumatoid arthritis but is different from any of the syndromes described, in that there is no ankylosis of the joints and apparently little damage to the joint surfaces (Fig. 4). On the other hand, the joint capsules seem exceedingly lax. The involvement of other body cartilages than joints is widespread and seems to be unique. The photograph in profile shows the changes in the external ear and in the nose (Fig. 1). The photographs and roentgenograms of the joints indicate the extreme laxness of capsular ligaments and the multiple dislocations (Figs. 2 and 3). The eyes have both become entirely blind following iridocyclitis, extreme hypotony, and degenerative changes of the structures within.

PRIMARY CARCINOMA OF THE TRACHEA

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AND
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PRIMARY carcinoma of the trachea is one of the rarest neoplasms found in man. Postmortem studies show the same paucity of cases at leading medical centers [1] throughout the world.

At McGill University Hospital,[1a] one case of carcinoma of the trachea was observed in 9,000 autopsies; at Montreal Hospital,[1a] one case in 12,700 autopsies; at Johns Hopkins University Hospital,[1a] Baltimore, no case in 15,000 autopsies; at New Haven Hospital,[1a] New Haven, Conn., no case in 3,900 autopsies; at Philadelphia General Hospital,[1b] two cases in 25,000 autopsies; at Charity Hospital,[1b] New Orleans, one case in 23 years; at Los Angeles County Hospital,[1b] no case in 12,000 autopsies; at Cook County Hospital,[1b] Chicago, one case in 545 cases of carcinoma, and at Guy's Hospital, London,[1b] no case in 5,000 autopsies. Fraenkel, whose work is cited by Stenn,[1b] reported seven cases in 5,063 autopsies, an incidence of 1.4%, which is much higher than most others from the world's centers.

Because it is so rare, primary carcinoma of the trachea is not mentioned in many standard texts on general pathology,[2] nor is the condition described even in some of those on neoplastic diseases.[3] This is unfortunate because it is apparent from a review of recent literature, first, that the diagnosis of primary carcinoma of the trachea can be made ante mortem [4] and, second, that if the diagnosis is made in time the condition can be treated successfully.[5] It is for these reasons that we wish to report the following case.

From the Department of Medicine, Gouverneur Hospital.

1. (*a*) Culp, O. S.: Primary Carcinoma of the Trachea, J. Thoracic Surg. **7**:471-487 (June) 1938. (*b*) Stenn, F.: Carcinoma of the Trachea: Review of Recent Literature and Report of a Case, Arch. Otolaryng. **21**:190-198 (Feb.) 1935.

2. Boyd, W.: A Text Book of Pathology, Ed. 3, Philadelphia, Lea & Febiger, 1938. MacCallum, W. A.: A Text Book of Pathology, Ed. 6, Philadelphia, W. B. Saunders Company, 1938. Karsner, H. T.: Human Pathology, Ed. 6, Philadelphia, J. B. Lippincott Company, 1940.

3. Pack, G. T., and Livingston, E.: Treatment of Cancer and Allied Diseases, New York, Paul B. Hoeber, Inc., 1940. Ewing, J.: Neoplastic Diseases: A Treatise on Tumors, Ed. 4, Philadelphia, W. B. Saunders Company, 1940.

4. (*a*) Tinney, W. S.; Moersch, H. J., and McDonald, J. R.: Tumors of the Trachea, Arch. Otolaryng. **41**:284-290 (April) 1945. (*b*) Penta, A. Q.: Primary Carcinoma of the Trachea Removed by Bronchoscopic Procedure, Ann. Otol. Rhin. & Laryng. **56**:790-792 (Sept.) 1947. (*c*) Fisher, G. E.: Cancer of the Trachea: Report of 5 Cases, Arch. Otolaryng. **40**:49-51 (July) 1944. (*d*) Gilfoy, F. E.: Primary Malignant Tumors of the Lower Third of the Trachea: Report of a Case with Successful Treatment by Electrofulguration and Deep X-Rays, ibid. **16**:182-187 (Aug.) 1932. (*e*) Brown, J.; Weiss, H. B.; Iglauer, S., and Fine, A.: Carcinoma of the Trachea, Radiology **41**:394-397 (Oct.) 1943. (*f*) Pierson, P. H.: Primary Carcinoma of the Trachea: Treatment with Intratracheal Radium; Radioactive Iodine Fails to Show Thyroid Origin, J. A. M. A. **126**:206-209 (Sept. 23) 1944. (*g*) Engler, C. W.: Carcinoma of the Trachea, Ann. Otol. Rhin. & Laryng. **57**:429-443 (Jan.) 1948.

5. Footnote 4*a*, *b*, *d to g*.

REPORT OF CASE

H. S., a 66-year-old white Hebrew man, was admitted on Aug. 11, 1949, to the medical service of Gouverneur Hospital, with chief complaints of upper abdominal pain and daily hemoptysis of two weeks' duration.

About 20 years previously, following a respiratory infection, chronic bronchitis developed. In 1943 the patient was hospitalized at another institution with bronchial asthma, and he had had recurrent episodes of wheezing and dyspnea which required the aid of a physician. In 1945 he sustained a heart attack with substernal oppression. However, he refused to stay in a hospital and thereafter was subject to recurrent episodes of angina. He had a mild chronic cough which was occasionally productive of yellow sputum. About two weeks previous to admission, he began to have daily hemoptyses. He also noted that his urine was dark brown and his stools light yellow. There was no accompanying nausea or vomiting, but he had anorexia for two or three weeks. About two days before admission, a knife-like pain developed in the upper abdomen, which radiated laterally along the right subcostal margin, beginning at the inner aspect of the right upper abdominal quadrant. He had lost 90 lb. (40.8 kg.) in the last nine years. He was a heavy beer drinker until two months prior to admission but apparently ate normally. Five months before admission, he had 12 injections in treatment of asthma.

The physical examination showed that the patient was a fairly well-developed, well-nourished white man, dyspneic, in pain, and icteric. The pupils were round and equal and reacted normally. Funduscopy showed that the disks were not well defined, but the retinae appeared normal. The throat was clear. The tongue was in the midline. There was no cervical adenopathy, cervical mass, or neck vein distention. The chest was barrel-shaped and had diminished expansion. Tactile fremitus and percussion sounds were normal except for some dulness at the left base posteriorly. The breath sounds were loud, and there was a prolonged expiratory phase bilaterally, with musical rales and rhonchi. The point of maximum impulse was 1 fingerbreadth outside the midclavicular line and in the fifth intercostal space. The heart sounds were diminished by the respiratory sounds. The rhythm was regular. The second pulmonary sound was greater than the second aortic sound, and there was a rough first aortic sound. The liver was felt 2 fingerbreadths below the costal margin and across the upper abdomen. It was firm and exquisitely tender. The spleen and kidneys were not palpated. The external genitalia were normal. The prostate was moderately enlarged, semifirm, and smooth. There was no clubbing of the upper extremities and only minimal pretibial edema in the lower. There were a few spider angiomata over the chest, and the axillary hair was sparse.

The clinical impression at the time of admission was that the patient had bronchial asthma, chronic bronchitis, bronchiectasis, and homologous serum hepatitis.

Laboratory Data.—The following tests gave normal results: the Wassermann tests, prothrombin time, blood urea nitrogen and sugar determinations, and cephalin flocculation. All urine specimens but one, which had a faint trace, showed an absence of bile and the presence of urobilinogen in a 1:10 dilution. The venous pressure was 88 mm. of water, with no change on hepatic pressure. The arm-to-tongue circulation time was 12 seconds.

Sputum analyses were negative for malignant cells and tubercle bacilli. The urine was alkaline, cloudy, and dark red-brown. The specific gravity was 1.004. There was no albumin or sugar present. The microscopic examination showed amorphous phosphates and occasional red and white blood cells. The red blood cell count was 4,500,000, with a hemoglobin concentration of 15 gm. per 100 cc. The white blood cell count was 10,500, with a differential count of 84% polymorphonuclear leucocytes, 14% lymphocytes, and 2% monocytes. The erythrocyte sedimentation rate was 20 mm. per hour with the Wintrobe technique. The blood total protein varied between 5.9 and 7 gm. per 100 cc., with an albumin-globulin ratio between 0.8 and 1.6. The total cholesterol was between 297 and 396 mg. per 100 cc., with a 21% esterification fraction. The van den Bergh test gave a strong positive direct reaction, and the serum bilirubin was 3.8 mg. per 100 cc. The alkaline phosphatase varied between 7.5 and 9 Bodansky units. Stool analysis was always negative for bile and on one occasion was reported as showing a 1+ reaction for occult blood.

An electrocardiogram revealed an intraventricular conduction defect and left axis deviation. A roentgenogram of the chest was suggestive of bronchiectasis. A liver biopsy specimen showed metastatic carcinoma.

Clinical Course.—While the patient was in the hospital, his temperature varied between 98 and 102 F. His liver progressively enlarged to a point 6 fingerbreadths below the costal margin and remained exquisitely tender. Marked sacral and peripheral edema developed, but no ascites. A paroxysmal cough, which would last for five minutes and then completely subside, was recurrent throughout his hospital stay. Occasionally the yellow sputum expectorated was blood-streaked.

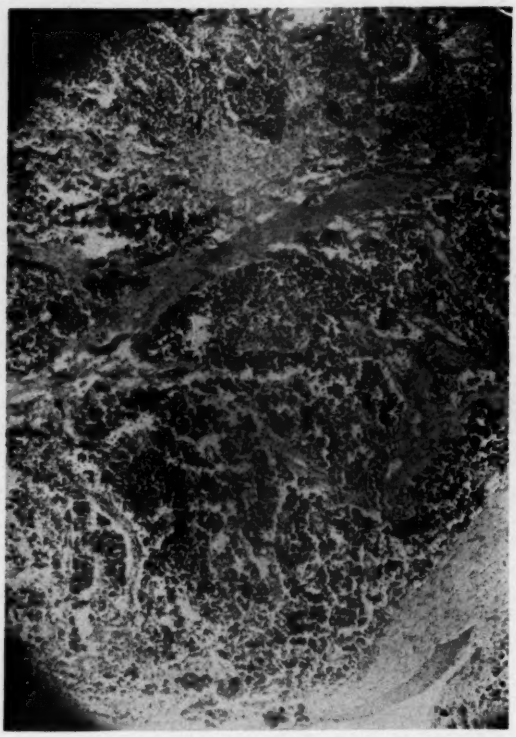

Fig. 1.—Photomicrograph of the primary tracheal tumor, showing sheets of small round cells. × 35.

The patient was treated with a high-carbohydrate, high-protein, high-vitamin diet, but his course went rapidly downhill, and he died on Sept. 11, 1949.

Autopsy Observations.—Gross Description: Heart: The heart weighed 390 gm. and showed some generalized dilatation. A mild degree of subendocardial fibrosis in both ventricles and sclerosis of the aortic valve were present. On cut section the myocardium contained streaks of gray tissue. The coronary arteries were widely patent and contained some atherosclerotic plaques.

Trachea: In the upper third of the trachea and on its posterior wall, the mucosa was seen to be irregularly elevated in an area about 3 cm. in diameter. This area was soft, ulcerated, and hemorrhagic and extended into the adjacent normal mucosa. On cut section the tissue

was gray-white and contained flecks of yellow. This tissue could be seen extending through the posterior wall of the trachea and was visible on the outer surface.

Bronchi and lungs: The bronchi were considerably dilated in a cylindrical fashion down to the bases of the lungs, and the smaller rami contained red, gray, and yellow mucoid material. The parenchyma was emphysematous, and on cut section frothy fluid could be expressed. There was marked congestion. The small arteries were moderately prominent.

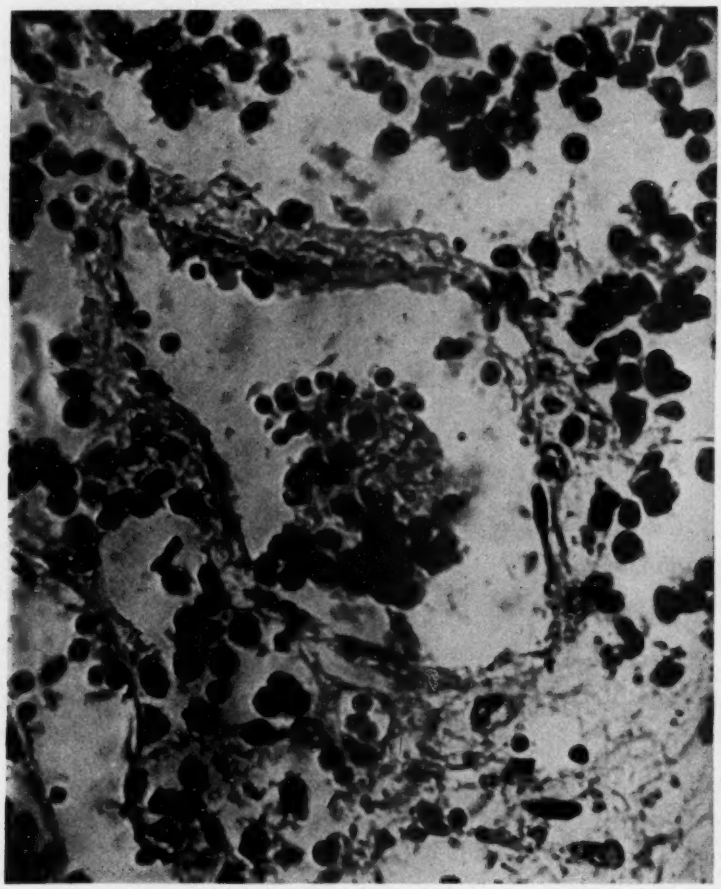

Fig. 2.—Photomicrograph, showing vascular spaces within the septa of the tumor containing tumor cells. × 500.

Lymph nodes: The cervical, peritracheal, and peribronchial lymph nodes were not unusual.

Gastrointestinal tract: There were no pathological changes in the esophagus, stomach, duodenum, jejunum, ileum, or colon.

Liver: The liver weighed 6,500 gm. The external surface was nodular and contained various-sized irregular umbilicated nodules, measuring up to 4 cm. in diameter. On section the majority of the parenchyma was replaced by these nodules, which had soft centers and a

gray-yellow periphery. The entire extrahepatic biliary tree was patent. There was marked constriction of the lumen of the inferior vena cava as it passed adjacent to the right lobe of the liver.

The pancreas, spleen, kidneys, and adrenal glands were not abnormal.

Microscopic Description: Trachea: This section was directly through the tumor and showed sheets of small, deeply basophilic round cells (Fig. 1) which exhibited some degree of pleomorphism and hyperchromatism. These resembled the oat cells which occur in tumors in

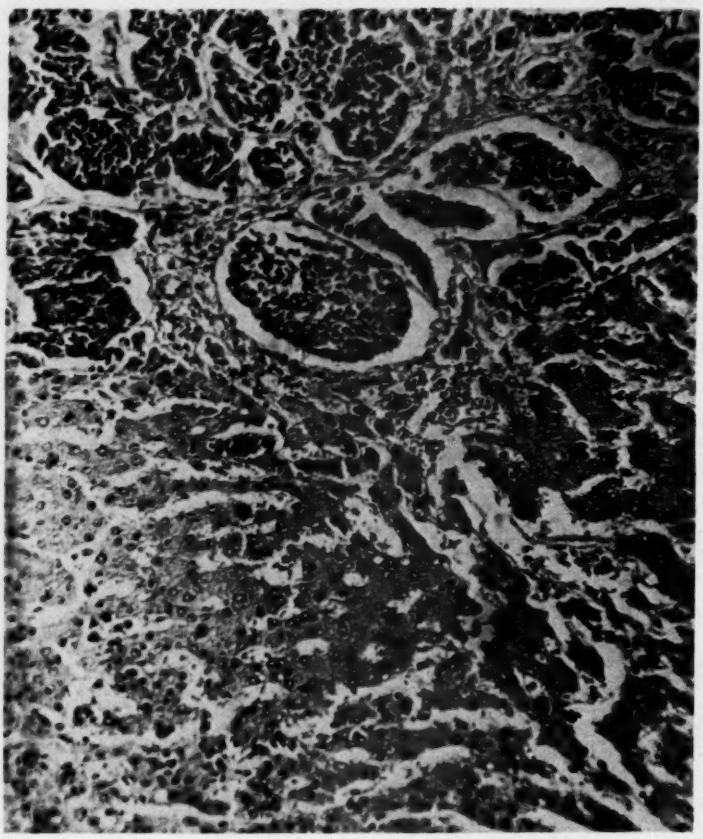

Fig. 3.—Photomicrograph of liver, showing sheets of tumor cells within lymphatic spaces and sinusoids. × 350.

the lower bronchial tree. Some of these sheets were separated by thin septa of fibrous connective tissue. There was no degree of differentiation within the tumor. Within the many vascular slits in the fibrous septa could be seen groups of the tumor cells (Fig. 2). In the same section was a portion of the esophagus showing tumor tissue extending into the submucosa and up to the surface lining of stratified squamous epithelium. However, the tumor cells did not reach the surface at any point.

Liver: This section showed various-sized nests of small, deeply basophilic round cells lying in the liver. These nests could be seen within lymphatic spaces in the portal areas

(Fig. 3). Around the central veins the liver cells were vacuolated, and there were small round and linear bile thrombi in the bile canaliculi. The sinusoids were dilated, and some were filled with red blood cells and tumor cells. The Kupffer cells were not prominent. The overall lobular architecture was disturbed by large nests of tumor cells which spread out from the portal areas. The bile ducts in these areas were not dilated.

Portal lymph nodes: These nodes were completely replaced by numerous colonies of small, round epithelial cells, similar to those seen in the liver.

Lung: The pleura was broadened and consisted of dense fibrous connective tissue. The alveoli were markedly dilated and in many cases disrupted so that they formed large spaces. The interalveolar septa were for the most part disrupted, stretched, and thinned, and they contained many dilated congested blood vessels. The bronchioles contained denuded, desquamated mucosal surfaces, with collections of plasma cells and lymphocytes in the submucosa. The capillaries in the walls of the bronchioles were markedly congested. The basement membrane was irregularly interrupted. The larger blood vessels were extremely dilated, and their walls were thickened.

Heart: The coronary vessels showed considerable intimal thickening. The myocardium contained many areas of linear fibrous connective tissue separating and replacing normal muscle tissue.

The kidneys, adrenal glands, pancreas, testes, small and large intestine, and spleen were not unusual.

Anatomic Diagnoses (Partial).—The anatomic diagnoses were as follows: Primary undifferentiated carcinoma of the trachea; liver and periportal lymph nodes with metastatic carcinoma; chronic bronchitis; pulmonary emphysema and cylindrical bronchiectasis; pulmonary arteriosclerosis; pulmonary edema; myofibrosis cordis and coronary sclerosis; generalized icterus.

COMMENT

I. *Incidence.*—In 1933 Simpson and Moore [6] reported 33 cases of carcinoma of the lower third of the trachea. Fisher [4c] in 1944 stated that there were 60 cases of carcinoma of the trachea in the literature up to 1924 and 154 cases by 1933. Culp [1a] in 1938 found 147 cases (only 82 of which had accurate histologic descriptions according to Tinney [4a]). Olsen [7] stated four cases were added up to 1939, and he presented nine additional cases. Since then and up to the present sporadic cases have been added to the world literature, but the total remains under 200.

Sex: The majority of cases have been reported in males. Among 116 cases with data collected by Olsen, [7] 73 were of males and 43 of females. Among 27 cases involving the lower third of the trachea, Simpson [6] found 17 of males and 10 of females.

Age: Most patients were 40 to 65 years of age, and 90% were 30 to 70 years old.

II. *Pathological Aspects.—A.* Location: Most of the tumors originate in the lower third of the posterior wall. According to Olsen,[7] half of the growths occur in the lower third, one-third in the upper third, and one-sixth in the mid-third. He offers the explanation that the region of bifurcation is most easily traumatized and, therefore, most apt to develop carcinoma. The posterior wall is predisposed by its wealth of glands. The mid-third is least subject to irritation, being immobile, and is the least subject to carcinoma.

6. Simpson, W. L., and Moore, R. M.: Primary Colloid Adenocarcinoma of the Lower Third of the Trachea, Ann. Otol. Rhin. & Laryng. **43**:1133-1138 (Dec.) 1934.

7. Olsen, A. M.: Carcinoma of the Trachea, Arch. Otolaryng. **30**:615-630 (Oct.) 1939.

B. Histology of the Trachea: The trachea is lined by a mucous membrane of striated ciliary epithelial cells and goblet cells. Beneath the membrane are tubular alveolar glands. Beneath these glands the anterior two-thirds of the trachea contains hyaline cartilage surrounded by smooth muscle which encircles the tracheal tissue, blood vessels, and lymphatics.

C. Types of Tumors: Dean [8] speaks of three types of tumors arising from the basal layer of the respiratory epithelium—squamous, columnar, and glandular. He also describes a mixed tumor, similar to the mixed tumor of the parotid gland. Carcinoma of the trachea may resemble the basal-cell carcinoma of skin, and it may appear as a malignant adenoma, arising from the basal layer, the mucous glands, or their ducts.

Tinney divides tracheal tumors into four groups:

1. Squamous cell carcinoma, which constituted 40% of the cases seen at the Mayo Clinic. These tumors occur as papillary growths *in situ* or as infiltrating neoplasms.

2. Cylindroma (arising from mucous glands), which occurred in 8 of 27 cases at the Mayo Clinic. There is considerable confusion regarding the nature and classification of this tumor. While it is listed as benign by Eggston and Wolff,[9] Tinney and co-workers include 8 cases of cylindroma in their series of 27 malignant growths. Engler [4g] points out that in the literature a variety of names has been applied to to tumors with descriptions indistinguishable from that of cylindroma. It is, therefore, probable that a number of cases of cylindroma have been mistakenly labeled cases of mixed tumor of the salivary gland, adenoma, and even basal cell carcinoma.

3. Adenocarcinoma, of which there were six in the Mayo series, most of them anaplastic.

4. Hemangioendothelioma, a malignant although slow-growing vascular tumor. In the literature reviewed and to our knowledge, an oat-cell type of carcinoma, as this case displayed, has not been described.

D. Histogenesis: As with tumors elsewhere, authorities differ concerning the origin of carcinoma of the trachea. Some believe carcinoma cells arise from undifferentiated epithelium by metaplasia. Olsen [7] and others object to the term metaplasia because adult cells do not become transformed. It is during the stage of maturation that irritants may alter the direction of development. It is for this reason that many authors maintain that tumors originate in the multipotential basal cells which can give rise to all cell types.

E. Metastases: Carcinoma of the trachea metastasizes rapidly and occasionally widely.

1. Frequency: Stenn,[1b] in reviewing the literature in 1935, stated that metastases occurred in more than 50% of the cases. Although Robin and Mann (cited by Olsen [7]) asserted that even regional metastases are rare, the majority of authors report a high incidence of spread. For example, Simpson [6] found metastases noted in 62 of 91 case records he reviewed.

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8. Dean, W. L., Jr.: Adenocarcinoma of the Trachea: Pathological Classification of Assistance in Treatment and Prognosis, Ann. Otol. Rhin. & Laryng. **53**:669-678 (Dec.) 1944.

9. Eggston, A. A., and Wolff, D.: Histopathology of the Ear, Nose and Throat, Baltimore, Williams & Wilkins Company, 1947.

2. Sites: Almost every organ in the body has been reported as the site of metastases from carcinoma of the trachea. Keeney,[10] in reporting a case with skin infiltration, lists metastases to 10 viscera. Direct invasion is the most frequent and clinically the most significant, producing many of the presenting symptoms and signs (dysphagia, hoarseness, lump in the neck). Distant metastases, while not common, do occur and may influence the clinical picture (hepatomegaly, skin nodules, recurrent laryngeal paralyses).

In Keeney's case there were metastases to skin, mesentery, liver, gall bladder, spleen, pancreas, adrenal gland, kidney, vertebrae, lymph nodes, and prostate. Breslich [10a] lists metastases in the following order of frequency: (1) peritracheal region; (2) cervical and tracheobronchial nodes; (3) lung; (4) liver; (5) supraclavicular and axillary nodes, and (6) esophagus, spleen, pancreas, kidney, bone.

III. *Clinical Picture.—A.* Signs and Symptoms: As a result of differences in the position, size, and activity of tracheal carcinoma, the signs and symptoms are variable, and there is accordingly no single pathognomonic feature.

The signs and symptoms are determined by the tumor's mechanical interference with tracheal function rather than by its histologic structure. As shown by Moersch,[11] if the tumor is fixed to the tracheal wall by a wide base and causes constant partial obstruction to air flow, the patient has respiratory stridor. If the tumor hangs free from a pedicle, it may obstruct the trachea intermittently; if it obstructs on inspiration, it will produce atelectasis, while, if it obstructs on expiration, it will produce emphysema. Other frequent symptoms are caused by irritation and ulceration of the mucosa and invasion of the esophagus and the recurrent laryngeal nerves.

The onset of symptoms is often insidious. Culp,[1a] in reviewing the literature listed as the commonest symptoms (1) tickle in the throat, (2) irritating cough, and (3) persistent hoarseness. In some patients, all three are absent and dyspnea or hemoptysis is prominent. Jackson [12] listed wheeze, nocturnal dyspnea, dyspnea on exertion, and dysphagia as the chief symptoms. Moersch [11] found that in the 27 cases at Mayo Clinic dyspnea was the earliest and most outstanding symptom. It was present in 90% (24) of the cases. Dyspnea may be constant or paroxysmal. Nocturnal dyspnea is frequent and often is mislabeled as asthmatic in origin. Wheeze was common in Moersch's series, being present in 63% (16). Cough was present in 25% (18); cough is dry at first and later productive. It is often the first symptom noted and was important in 56% (15) of the Mayo Clinic series. Hemoptyses occurred in 44% (12). Pain is infrequent. Other symptoms include fever, dysphagia, and weight loss (late).

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10. Keeney, E. L.: Primary Carcinoma of the Trachea with Cutaneous Carcinomatosis, Bull. Johns Hopkins Hosp. **61**:411-420 (Dec.) 1937.

10a. Breslich, P. J.: Squamous Cell Carcinoma of Trachea, J. Cancer Research **14**:144-151 (March) 1930.

11. Moersch, H. J.; Tinney, W. S.; McDonald, J. R., and Clagett, O. T.: Symposium on Certain Tumors of the Bronchi (Adenomas and Cylindromas) and on Tumors of the Trachea, Proc. Staff Meet., Mayo Clin. **21**:410-428 (Oct. 30) 1946.

12. Jackson, C.: Tumor of the Trachea, South. Surgeon **5**:263-276 (Aug.) 1936.

B. Course: The course varies with the type, activity, and location of the tumor, as shown above in the genesis of the clinical picture.[13] The duration without treatment varies from weeks to a few months, but some tumors may grow slowly over the course of years.[4d] Death is due to suffocation, pneumonia, and hemorrhage, or metastatic complications.

C. Differential Diagnosis: The clinical picture may simulate that of most primary intrathoracic diseases. The conditions most frequently requiring differentiation are asthma, mediastinal tumor, carcinoma of the esophagus, emphysema, bronchiectasis, lung abscess, pneumonia, and thyroid enlargement.

D. Diagnosis: Any of the symptoms cited above as common in this disease—wheeze, dyspnea, hemoptysis—should arouse the suspicion of underlying respiratory tree lesions and the need for the establishment of a diagnosis. Gilfoy [4d] states that intermittent dyspnea with cough (with or without raising of blood) in an apparently healthy person without signs of intrathoracic disease spells carcinoma of the trachea.

While some suspicion of this rare condition can be gathered from the history and results of physical examination, it is by means of roentgenography and especially endoscopy that the diagnosis can be made. On the posteroanterior roentgen view mediastinal enlargement may be seen which on the lateral view can be recognized as a tracheal mass. Tomography may be of further benefit in detecting and localizing a tracheal mass.[14]

Bronchoscopy is the only certain means of diagnosing carcinoma of the trachea ante mortem.[11] Although carcinoma of the trachea is extremely rare, the diagnosis has been made with fair frequency [15] when the index of suspicion has been high.

IV. *Prognosis.*—The majority of patients die in one-half to one and one-half years. Most diagnoses are made either post mortem or too late ante mortem. Because of the tendency for the tumor to obstruct early in its course, the lesion is usually inoperable when visualized. The best outlook is for tumors of the upper third of the trachea because they are much more accessible to the surgeon.

V. *Treatment.*—Results: Thus far treatment has been largely unsatisfactory as indicated above. Among 38 patients whose cases are reported in the literature, Olsen [7] found 19 living, 2 having lived more than one year. Of the 19 still alive, 14 had lesions in the upper third of the trachea and 5 in the lower third. At the Mayo Clinic,[11] in a series of 15 patients, 7 were dead within 11 months and 7 were alive from 9 months to 9 years. One was alive more than nine years. Apart from the location of the tumor, its activity was an obviously major factor.

Methods: In tumors of the upper trachea tracheal fissure and electrocoagulation are generally accepted methods of treatment, since resection gives no better results. In tumors of the lower trachea electrocoagulation is used, some operators adding radon seeds.

13. Moersch and others.[11] Figi, F. A.: Primary Carcinoma of the Trachea, Arch. Otolaryng. **12**:446-456 (Oct.) 1930.

14. Ellman, P., and Whittaker, H.: Primary Carcinoma of the Trachea, Thorax **2**:153-162 (Sept.) 1947.

15. Fisher.[4e] Moersch and others.[11]

In all cases regional nodes are irradiated. In extensive carcinoma x-ray treatment is preferred to surgical measures.

Prospects: Despite the over-all poor results, there is an encouraging note in the fact that a number of cures have been achieved.[5] In cases in which early diagnosis is made, there is a reasonable prospect of cure. It is, therefore, true that in carcinoma of the trachea, as in carcinoma elsewhere, early diagnosis is essential. Because it is a rare neoplasm, it is not often considered and less often diagnosed. The methods of diagnosis are discussed above. Emphasis is laid on the fact that methods for diagnosis and treatment are available.

The case presented in this report is interesting from several points of view:

1. This seems to be the first undifferentiated carcinoma, similar to an oat-cell type, which has ever been described in the upper third of the tracheobronchial tree.

2. Tumor cells observed in the hepatic sinusoids and in draining lymphatic spaces and portal lymph nodes, without any direct peritracheal or mediastinal lymph node involvement, might indicate that the route of spread to the liver was hematogenous.

3. The progressive peripheral and sacral edema was due simply to obstruction of the inferior vena cava by an enlargement of the liver, thereby reducing normal venous return from the lower portions of the body.

4. Since this patient had coughed for many years, it is difficult to say how long the tumor had been present. However, from its small size and the onset of hemoptysis two weeks before admission, we feel that it was of recent origin, and the rapid downhill course of the patient, with massive liver metastases, tends to confirm the previous concept of a hematogenous dissemination.

5. The case initially presented two factors that led us away from the diagnosis: (*a*) the history and findings of chronic pulmonary disease, which could have accounted for all the pulmonary symptoms, and (*b*) the history of a series of injections for asthma given five months previously, which could have produced the clinical entity of homologous serum hepatitis.

SUMMARY

A case is presented of a primary carcinoma of the trachea. The entire subject is reviewed, and the individual characteristics of this case are presented.

2018 E. 27th St., Brooklyn 29 (Dr. Zarowitz).

Dr. Arthur Shifrin, of Mount Sinai Hospital and Gouverneur Hospital, New York, gave constructive criticisms, and Dr. David M. Grayzel and Dr. Abraham Mackles, pathologists at the Jewish Hospital of Brooklyn, reviewed the slides.

Progress in Internal Medicine

SYPHILIS

A Review of the Recent Literature

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(Concluded from Page 352)

GENERAL THERAPY OF SYPHILIS

FROM the maze of articles appearing on the therapy of syphilis, a crystallization of opinion is being evolved. It would take more space than is available or advisable to cover in detail the various techniques of treatment. We will, therefore, merely refer to the interested reader some of the numerous discussions,[183] and detail

183. Johnwick, E. B.: Experiences with Penicillin in Syphilotherapy, Rocky Mountain M. J. **47**:931-926 (Dec.) 1950. Rosen, I., and Sobel, N.: Fifty Years' Progress in the Treatment of Syphilis, New York J. Med. **50**:2694-2696 (Nov. 15) 1950. Curtis, A. C.: Symposium on Dermatology: Modern Therapy of Syphilis, Mod. Med. **18**:90-92 (Nov. 15) 1950; Modern Therapy in Syphilis, Chicago M. Soc. Bull. **53**:49-50 (July 22) 1950; Penicillin and Syphilis, Correspondence, J. A. M. A. **144**:947-948 (Nov. 11) 1950. Cooper, G. A.: Diagnosis and Treatment of Syphilis, Wisconsin M. J. **49**:911-914 (Oct.) 1950. Lees, R.: Chemotherapy of Venereal Diseases: Its Uses and Abuses, Brit. J. Ven. Dis. **27**:34-37 (March) 1951. Laird, S. M.: Chemotherapy of Venereal Diseases: Its Uses and Abuses, ibid. **27**:38-40 (March) 1951. Walker, S. A., and Stoughton, R. B.: Modern Trends in Syphilis Therapy, M. Clin. North America **35**:143-152 (Jan.) 1951. Thomas, E. W.: Modern Treatment of Syphilis, Bull. New York Acad. Med. **27**:175-183 (March) 1951. Vogel, H. R.: The Role of Antibiotics in the Modern Treatment of Syphilis, Pennsylvania M. J. **54**:234-236 (March) 1951. Brunsting, L. A.: The Present Status of the Problem of Syphilis, J. Michigan M. Soc. **50**:48-53 (Jan.) 1951. Keefer, C. S.: Evaluation of Antibiotic Therapy, Postgrad. Med. **9**:101-105 (Feb.) 1951. Kogoj, F.: Penicillin als Antisyphilitikum, Arch. Dermat. u. Syph. **191**:343-350, 1950. Moncorps and Heite: Experimentelle und klinische Studien über die antiluische Penicillinbehandlung bei Kombination mit Arsenobenzolen und Wismut, ibid. **191**:446-450, 1950. Miescher, G.: Chemotherapeutica und Antibiotica in der Behandlung von Haut- und Geschlechtskrankheiten: Klinische Anwendung bei Syphilis, ibid. **191**:267-292, 1950. Haxthausen, H.: Penicillin Treatment of Syphilis: Review, Ugesk. læger **112**:1375-1377 (Oct. 5) 1950. Tucker, H. A.: Symposium on Medical Therapeutics: Present Status of the Treatment of Syphilis, M. Clin. North America **34**:495-507 (March) 1950. Hellerstrom, S.: Les conceptions actuelles de la thérapeutique antisyphilitique en suéde, Maroc méd. **29**:1009-1014 (Nov.) 1950. Langer, E.: Penicillinbehandlung der Syphilis, Ärztl. Wchnschr. **6**:193-197 (March 2) 1951. Gottlieb, D., and Long, P. H.: Second Italian Congress on Antibiotics, Foreign Letters, J. A. M. A. **143**:1443 (Aug. 19) 1950. Thompson, W. C.: Present Tendencies in Antibiotic Therapy, Mississippi Doctor **28**:93-96 (Aug.) 1950. Epstein, N.: The Treatment of Syphilis, Am. Pract. **2**:317-319 (April) 1951.

the schemes of therapy for syphilis as advised by a representative committee of experts from the United States. Curtis and a country-wide group of syphilologists [184] have attempted to formulate specific treatment schedules which they recommend for the various phases of syphilis. Although no documentation for the recommended systems is appended, this hand-picked group has tried to reflect the consensus of the literature along with their personal viewpoints. The dosage schedules compiled are as follows:

Treatment Schedule *

Type of Syphilis	Dosage
Early	
Primary	2,400,000 units at first treatment (may be divided equally in both buttocks), followed by 4 injections at 4-day intervals of 600,000 units each
Secondary	
Latent	
Late	
Osseous	6,000,000 units: 600,000 units daily for 10 days, or 600,000 units twice weekly for 5 weeks
Cutaneous	
Visceral	
Mucous membrane	
Cardiovascular	
(No decompensation)	
Neurosyphilis (All types)	6,000,000 to 12,000,000 units: 600,000 units daily or twice weekly
Pregnancy	4,800,000 units:
1st or 2d trimester	600,000 units twice weekly for 4 weeks or 1,200,000 once a week for 4 weeks
3d trimester	600,000 units daily for 8 days
If labor is imminent	2,400,000 units at one time; repeat in 1 week if patient has not delivered
For relapse cases	900,000 units once a week for 4 weeks (3,600,000 units)
Congenital	
Early	Either of the following 3 schedules:
(Less than 2 years)	1. 10,000 units per pound of body weight daily for 10 days 2. 15,000 units per pound of body weight twice weekly for 4 weeks 3. 40,000 units per pound of body weight once a week for 4 weeks
Late	6,000,000 units:
(More than 2 years)	600,000 units daily or twice weekly
Prophylaxis	1,200,000 units in one treatment

* If response is unfavorable, a second course similar to the first may be given following a six- to eight-week rest period.

In connection with Schedules 1, 2, and 3 listed in the table or Schedules A, B, and C as given in the text, respectively, under "Early Congenital Syphilis," Shaffer in a personal communication stated:

Schedule A states "10,000 units per pound of body weight of procaine penicillin in oil or aqueous suspension administered daily for 10 days." I should have stated that this was the recommended dose for each injection in all the schedules mentioned, rather than total dosage. If you gained the impression that it was total dosage undoubtedly others will.

Schedule B should have read "15,000 units per pound of body weight per injection given twice weekly for four weeks, and the 40,000 units per injection given once weekly for four treatments."

In each of these three schedules, therefore, there would have been a total dosage per pound of 100,000, 120,000, and 160,000 units, respectively.

184. Curtis, A. C.; Kitchen, D. K.; O'Leary, P. A.; Rattner, H.; Rein, C. R.; Schoch, A. G.; Shaffer, L. W., and Wile, U. J.: Penicillin Treatment of Syphilis, J. A. M. A. **145**:1223-1226 (April 21) 1951.

Bruetsch [185] believes that the Curtis group's recommendation of a minimum dose of 6,000,000 units of penicillin for neurosyphilis, or a total of 6,000,000 units for cardiovascular syphilis, is an inadequate total dosage for completely successful therapy. Granting possible exceptions, the treatment schedules are a reasonably acceptable present-day guide for the practitioner.

PENICILLIN THERAPY OF SYPHILIS

The pharmacology of penicillin, so far as it affects syphilotherapy, has received considerable study during this review period. For general orientation, Keefer's [186] article is recommmended. He discusses the problem from the standpoints of antibiotics, mode of action, synergistic effects, specific diseases treated with them, and hypersensitivity. Antibiotics in order of discovery are tyrothricin, penicillin, streptomycin, bacitracin, polymyxin, aureomycin, chloramphenicol, neomycin, and terramycin. Huriez [187] discusses the possibilities and limitations of the various methods of so-called retard penicillin therapy. Studies are reported by Boger and his co-workers [188] which demonstrate that a new compound, *p*-(di-*n*-propylsulfamyl)-benzoic acid ("benemid"), is capable of increasing by two- to fourfold the plasma concentrations of both penicillin and *p*-aminosalicylic acid (PAS). No evidence of local or systemic toxicity was observed in any of the patients studied.

Synergistic Action and Potential Applications of Antibiotic Combinations.—Romansky and his co-workers [189] present evidence showing increasing resistance of various strains of bacteria to the available antibiotics. Antibiotic combinations, in vitro, exhibit synergistic action against some strains of bacteria. Preliminary clinical studies show promise in the use of antibiotic combinations. The availability of the newer antibiotics and the use of the antibiotic combinations make necessary more careful bacteriological control in the clinical management of infections. No specific mention of the applicability of this problem to syphilis is made, but the inference is clear.

Action of Penicillin on T. Pallidum.—As a result of their studies, Frankl and Koranyi [190] noted that if syphilitic lesions were treated locally with penicillin there was a definite demonstrable effect, the number of spirochetes decreased and the motility decreased and disappeared after an hour. A single injection of penicillin (40,000 units intramuscularly) is active in a syphilitic. Funk and Walther [191] also

185. Bruetsch, W. L.: Penicillin Treatment of Syphilis, Correspondence, J. A. M. A. **146**:396 (May 26) 1951.

186. Keefer, C. S.: Antibiotics: Yesterday, Today, Tomorrow, Ann. Int. Med. **33**:582-589 (Sept.) 1950.

187. Huriez, C.: Possibilités et limites des divers procédés—dits retard—de pénicillothérapie, Arch. belges dermat. et syph. **6**:274-283 (Dec.) 1950.

188. Boger, W. P.; Beatty, J. O.; Pitts, F. W., and Flippin, H. F.: The Influence of a New Benzoic Acid Derivative on the Metabolism of Para-Aminosalicylic Acid (PAS) and Penicillin, Ann. Int. Med. **33**:18-31 (July) 1950.

189. Romansky, M. J.; Fusillo, M. H.; Caldwell, E., and Robin, E. D.: The Synergistic Action and Potential Applications of Antibiotic Combinations, M. Clin. North America **35**:535-544 (March) 1951.

190. Frankl, J., and Koranyi, B.: Über die Wirkung des Penicillins auf die Spirochaeta pallida, Arch. Dermat. u. Syph. **190**:50-56, 1950.

191. Funk, C. F., and Walther, H.: Beitrag zur raschen Penicillinwirkung auf die Syphilisspirochäten durch feingewebliche Untersuchungen, München. med. Wchnschr. **92**:1427-1431 (Dec. 8) 1950.

were impressed with the rapid effect of penicillin on T. pallidum. They treated an infant 23 days old having congenital syphilis with crystalline procaine penicillin G and buffered crystalline potassium penicillin G in aqueous solution in dosage of 2,500 units twice daily, which was increased to 10,000 and 20,000 units for a total dosage of 95,000 units. The patient died from circulatory collapse on the 13th day of treatment. At autopsy, in spite of a healing syphilitic osteochondritis, no T. pallidum could be found in the organs examined by the Levaditi stain.

Placental Transmission of Procaine Penicillin G in Oil with Two per Cent Aluminum Monostearate.—Animal and human studies have demonstrated the placental transfer of penicillin from maternal to the cord blood following its injection ante partum. The placentally transmitted penicillin has been found in the amniotic fluid. However, penicillin from various preparations apparently does not cross the placenta with equal facility or with predictable constancy. Placental passage of penicillin was first discussed in a review of blood-barrier sites. Herrell and co-workers reported studies on three pregnant women at term. The significance of this type of study to syphilotherapy during pregnancy prompted Woltz and Wiley to investigate the transmission of penicillin to the previable fetus. The antibiotic was found to reach the fetus as early as 10 weeks after conception. Penicillin was administered by either the intravenous or the intramuscular route. The advantages of immediate antepartum penicillin therapy have been stated by Hutter and Parks. They advocate antepartum use of penicillin therapeutically in syphilis and gonorrhea of pregnancy and prophylactically in patients with prolonged rupture of the membranes. The latter precaution guards against puerperal infection in the mother and intrauterine pneumonia in the fetus. Kitchen and his co-workers[192] studied 181 normal women who delivered their babies within 15 hours after the injection of 300,000 units of procaine penicillin G in oil with 2% aluminum monostearate (1 cc. intramuscularly). Assay of maternal and cord blood, drawn at delivery, has been compiled and the relationship between infant and maternal blood levels studied with respect to the elapsed time between injection and delivery. Grasset and co-workers[193] administered 300,000 units of crystallized penicillin G by the intramuscular route to 15 pregnant women. Duration of the pregnancy varied from six weeks to full term. Delivery of the fetus by Caesarean section was performed in six instances, while pregnancy was interrupted by an abdominal hysterotomy for various conditions in nine instances. Consequently, the exact interval between the penicillin injection and the removal of the fetus could be determined. It varied from 30 minutes to two hours. Determination of the penicillin concentration in the maternal and fetal circulation, in the fetal organs, and in the amniotic fluid showed that transplacental passage of penicillin was limited in all instances. The penicillin concentration in the fetus was nevertheless sufficiently high to insure an effective antibiotic action against various micro-organisms sensitive to penicillin, particularly against T. pallidum. These results confirmed those obtained by the authors in

192. Kitchen, D. K.; Speiser, M. D.; Spoor, H. J.; Rein, C. R., and Thomas, E. W.: Placental Transmission of Penicillin Following Single Injections of Procaine Penicillin G in Oil with 2 per Cent Aluminum Monostearate (300,000 Units): Maternal and Cord Blood Concentrations, Antibiotics & Chemotherapy **1**:110-112 (May) 1951.

193. Grasset, E.; de Watteville, H., and Dossena, P.: Passage transplacentaire de la pénicilline au cours de la grossesse, Schweiz. med. Wchnschr. **80**:841-844 (Aug. 12) 1950.

experiments on rabbits and guinea pigs and those obtained by other investigators on the permeability of the placental barrier to penicillin. The permeability does not vary much from two months to the full term of gestation; effective antisyphilitic treatment, therefore, may be instituted at any stage of pregnancy. Concentration of penicillin in the maternal blood should be fairly high to insure a minimum spirocheticidal level in the embryo and to prevent the development of penicillin resistance in T. pallidum resulting from too small doses of the antibiotic.

Oral Penicillin Therapy.—Although their patients did not have syphilis, Bunn and his colleagues [194] demonstrated that oral penicillin therapy is convenient and effective when given in large doses (at least 500,000 units) twice or three times a day. A study by Boger and Beatty [195] of the blood samples from six healthy adult men after single oral 500,000-unit doses of various penicillins showed that aluminum, bismuth, and ferric salts, when orally administered, do not result in higher plasma concentrations than that following ingestion of potassium penicillin. Kitchen, Thomas, and Rein [196] compared the serum concentration following administration of highly compressed crystalline procaine penicillin G tablets with that following administration of lightly compressed ones containing a binder. The latter produced a much higher concentration and longer maintenance of the minimum therapeutic level than the former tablets, and results were comparable with the previous experiences with crystalline sodium penicillin G given in a similar amount. The difference was considered to be due to the unsatisfactory disintegration of the highly compressed tablets, which resulted in faulty utilization.

Penicillin Levels in the Blood: Significance of Various Factors.—It is well known now that the level of concentration of penicillin in the blood after various routes of administration is not merely a matter of the type of preparation used. When Cannon and his co-workers [197] set out to compare the efficacy of the various penicillin preparations as they became available, they found it necessary to evaluate the influence of kidney function and the relation of dose to weight on the height and duration of penicillin levels in the blood serum. Since the Cannon group's first report on this subject,[198] they studied 27 commercial preparations of penicillin in various absorption-delaying vehicles. The five preparations studied included crystalline penicillin in oil and wax; crystalline penicillin G procaine in oil; crystalline penicillin G procaine containing 2% (W/V) aluminum monostearate (micronized particles); crystalline penicillin G procaine in oil containing 2% (W/V) aluminum monostearate (micronized particles), and crystalline penicillin G procaine in isotonic

194. Bunn, P.; Caldwell, E. R.; Adair, C.; Lepper, M., and Dowling, H.: Absorption and Clinical Use of Penicillin Preparations Given in Large Oral Doses: A Cooperative Study Utilizing Discontinuous Therapy, J. A. M. A. **144**:1540-1543 (Dec. 30) 1950.

195. Boger, W. P., and Beatty, J. O.: Metallo-Penicillins: Plasma Concentrations of Penicillin After Oral Administration, Am. J. Clin. Path. **20**:1070-1075 (Nov.) 1950.

196. Kitchen, D. K.; Thomas, E. V., and Rein, C. R.: Serum Concentration Following the Oral Administration of Crystalline Procaine Penicillin G, J. Invest. Dermat. **14**:229-231 (April) 1950.

197. Cannon, A. B.; Slatkin, M. H.; Chester, B., and Moses, R.: Penicillin Levels in the Blood: Significance of Type of Preparation, Dosage, Kidney Function and Weight, J. A. M. A. **145**:1031-1034 (April 7) 1951.

198. Cannon, A. B.; Lindstrom, K.; Bradley, D. F.; Slatkin, M. H., and Moses, R.: Penicillin in Sesame Oil and Wax: Observations on Delayed Absorption in 65 Patients. J. Invest. Dermat. **9**:255-259 (Nov.) 1947.

sodium chloride solution. Six hundred twenty-eight patients, male and female, Negro and white, ambulatory and hospitalized, were given these penicillin preparations. The ages ranged from 16 to 70. Most of the patients had syphilis. The authors found that impaired kidney function, as shown by the Fishberg concentration test, produces higher and more prolonged penicillin blood levels. They suggest that in order to arrive at a base line for comparison of the various penicillin products, this factor should be considered. It is suggested that the dosage of repository penicillins be adjusted so that the patient receives at least 3,000 to 6,000 units per pound (0.5 kg.) of body weight. It was found that the efficacy of various delayed-action penicillin preparations in prolonging the penicillin blood levels was in the following order: (1) penicillin procaine with aluminum monostearate (micronized particles), (2) penicillin procaine with 2% aluminum monostearate (micronized particles) and penicillin procaine in oil, (3) penicillin procaine in aqueous solution, and (4) penicillin in oil and wax.

Blood Levels After Administration of Various Types of Depot Penicillin.—By comparing serum concentrations of penicillin after injection of various kinds of depot penicillin, Hasselmann and his co-workers [199] come to the conclusion that procaine penicillin G with 2% aluminum monostearate (flo-cillin®) gives the best results in maintaining a high blood concentration. Good results were also observed by using penicillin G in sesame oil (duracillin®). Ledercillin® shows, by adding crystalline sodium penicillin G to procaine penicillin G, an initial high blood level which is prolonged and declines slowly. Diminishing the amount of liquid had no influence on the absorption of ledercillin.® One parenteral injection of 200,000 units every 12 hours seemed to be sufficient in the treatment of syphilis. To use depomulgan® or penicillin in oil and wax is considered to be obsolete.

Constant Plasma Penicillin Level Produced by Daily Injections of Procaine Penicillin in Oil with Aluminum Monostearate.—Schaefer and Rashkoff [200] observed constant plasma levels of penicillin following a single daily intramuscular dose of procaine penicillin in oil with aluminum monostearate. After the fifth daily injection of 300,000 units, the levels averaged 0.5 unit per milliliter and did not fall below 0.2 unit per milliliter. A patient with bacterial endocarditis treated successfully with this preparation is described.

Procaine Penicillin: Choice of Preparation.—In order to determine the best procaine penicillin preparation with regard to ease of administration and capacity to sustain blood levels, Fairbrother and Daber [201] made assays of the penicillin blood levels in adults after intramuscular injection of two types of preparation, both with a particle size of 20 μ or less.

Penicillin Levels in Cerebrospinal Fluid After Intramuscular Injection of Procaine Penicillin.—Penicillin levels in the cerebrospinal fluid were determined by

199. Hasselmann, C. M.; Johne, H. O.; Legler, F., and Heinrich, S.: Experimentelle Untersuchungen über Blutspiegelkonzentration nach Depot-Penicillinen, Med. Klin. **45**:361-366 (March) 1950.

200. Schaefer, L. E., and Rashkoff, I. A.: Production of a Constant Plasma Penicillin Level by Means of Daily Injections of Procaine Penicillin in Oil with Aluminum Monostearate, J. Mt. Sinai Hosp. **16**:300-302 (Jan.-Feb.) 1950.

201. Fairbrother, R. W., and Daber, K. S.: Procaine Penicillin: Choice of Preparation. Brit. M. J. **1**:1098 (May 13) 1950.

Wright and his group [202] on 198 specimens taken from 114 patients at various time intervals after procaine penicillin in sesame oil containing 2% aluminum monostearate was injected intramuscularly in doses of 600,000 units every 24 hours for six doses. Of the 114 patients, 70 had spinal fluids negative for syphilis, 40 showed serologic evidence of neurosyphilis, and 4 were not tested for syphilis. Detectable levels of penicillin were obtained 2 to 290 hours after beginning the injections, with 82% showing a level at 31 hours and 91% at 122 hours. The highest concentration of penicillin was found 98 hours after the first injection, with a maximum of 0.074 unit per milliliter and an average of 0.21 unit per milliliter. A second group of 22 patients with early syphilis received one injection of 300,000 units of the same penicillin preparation. Levels were determined 24 and 72 hours after the intramuscular injection. Four of the specimens showed a measurable level of penicillin in the spinal fluid, 0.013 to 0.057 unit per milliliter, and eight showed a trace.

Two-Hour Versus Three-Hour Administration of Crystalline Penicillin G.—Bundesen and his colleagues,[203] in a series of 184 patients with dark-field-positive primary and secondary syphilis given 2,400,000 units of aqueous crystalline penicillin G in seven and one-half days, found that two- and three-hour intervals of administration of crystalline penicillin G in early syphilis are, for the purposes of therapeutic efficiency, of equal value. In another study 228 patients with dark-field-positive primary and secondary syphilis were each given 4,800,00 units of crystalline penicillin G in seven and one-half days by Plotke and his colleagues.[204] The cumulative failure rate regardless of diagnosis at the end of the 12 to 15 months' observation period was 13.7%. It appears that increasing the total dosage of crystalline penicillin G from 2,400,000 to 4,800,000 units in the treatment of early syphilis is of little significance in lowering cumulative failure rates. The article by Eagle, Fleischman, and Musselman [55] discussed in the section on experimental syphilis should be referred to in this connection.

Subcutaneous Implantation in Syphilis.—Results of subcutaneous implantation of procaine penicillin in 63 patients with syphilis are reported by Prunes, Weinstein, and Hevia.[205] Sixty adult patients each received 2,000,000 units of procaine penicillin (in a simultaneous implantation of two troches of 1,000,000 units apiece). The three remaining patients (children) had a single implantation of 1,000,000 units. In all cases spirochetes disappeared from the lesions within the first 24 hours, and the syphilitic lesions healed or disappeared within one or two weeks after penicillin implantation. Ten of the 11 patients with seronegative primary syphilis maintained negative serum reactions during the entire observation period, seven of them for more than seven months. One showed a transitory positive serologic

202. Wright, R. D.; Thayer, J. D.; Nicholson, F. P., and Arnold, R. C.: Penicillin Levels in Spinal Fluid After Intramuscular Injection of Procaine Penicillin, J. Ven. Dis. Inform. **32**:39-42 (Feb.) 1951.

203. Bundesen, H. N.; Rodriquez, J., and Schwemlein, G. X.: 2-Hour Versus 3-Hour Administration of Crystalline Penicillin G: The Treatment of Early Syphilis, J. Lab. & Clin. Med. **36**:759-762 (Nov.) 1950.

204. Plotke, F.; Rodriquez, J., and Schwemlein, G. X.: The Total Dosage Factor in the Use of Crystalline Penicillin G: The Treatment of Early Syphilis, Am. J. Syph. **35**:240-245 (May) 1951.

205. Prunes, L.; Weinstein, M., and Hevia, H.: Tratamiento de la sifilis en un solo tiempo, Rev. méd. Chile **79**:1-4 (Jan.) 1951.

reaction that subsided within one month. In all nine patients with seropositive primary syphilis the disease was controlled during an observation period of more than six months. Fifteen of 17 patients with secondary syphilis maintained negative serum reactions for more than four months. The fourth group of syphilitics who underwent procaine penicillin therapy included two adults with latent syphilis and five children with prenatal syphilis. Control of the disease was effected in all these patients on therapy without recurrences up to the present (more than nine months). The results of this study, on the basis of the 40 patients observed for more than four months, are satisfactory in all those with primary syphilis, in 82.7% of the patients with secondary syphilis, and in 80% of those with prenatal syphilis. Thus, the syphilis of 92.5% of all these patients responded favorably to procaine penicillin implantation therapy.

Penicillin and Arsphenamine.—Langer and his colleagues [206] made a study of the influence of penicillin and simultaneously administered arsphenamine (salvarsan). They believe that this relationship has important clinical implications. It is not known how and why the changes in penicillin occur. There seems to be an underlying chemical disturbance in the penicillin alone, or in the arsphenamine also, whereby an increase in toxicity occurs. From a practical standpoint there is no doubt that it is inadvisable to administer penicillin and arsphenamine simultaneously. It would probably be most desirable if one could give combined treatment with these two antisyphilitic agents so that the arsphenamine would follow the penicillin. However, in no case should the arsphenamine be administered simultaneously with the penicillin.

Histologic Reactions to Injections of Procaine Penicillin in Oil.—Story [207] found histologic changes in the deltoid muscles and adjacent lymph nodes of a patient who had received intramuscular injections of procaine penicillin in peanut oil. The preparation used contained 300,000 units of penicillin G combined with 120 mg. of procaine suspended in 1 cc. of peanut oil. The patient was a 67-year-old man who had received injections of the procaine penicillin for 24 days. No reaction was noted clinically at the sites of injection. At autopsy free oil was found in the muscle of each deltoid underneath the needle marks in the skin. The axillary lymph nodes were not enlarged. Histologic examination revealed that the affected areas of both deltoid muscles were edematous and that the perimysium contained oily globules. The oil occurred in small cysts surrounded by cellular reaction in which eosinophils were conspicuous. Numerous fat-bearing phagocytes were present around the oil. The axillary lymph nodes contained large numbers of foam cells which contained finely divided globules of oil.

TREATMENT OF EARLY SYPHILIS

Treatment of Early Syphilis with Penicillin.—Hitherto, confusion has existed regarding the proper place of penicillin in the treatment of syphilis. The possible reasons for this misinterpretation of the problems are discussed in a practical sum-

206. Langer, E.; Daeschlein, G., and Waterstraat, W.: Die Beeinflussung der Penicillinwirkung durch gleichzeitige Salvarsanangaben, Ztschr. Haut- u. Geschlechtskr. **9**:68-76 (July 15) 1950.

207. Story, P.: Histological Reactions to Injections of Procaine Penicillin in Oil, Brit. M. J. **1**:1467 (June 24) 1950.

mary presentation by Rein.[208] If we are to judge from the majority of reports in the literature to date, penicillin alone is the drug of choice in the therapy of early syphilis, and combined therapy with arsenic and bismuth appears to be of doubtful value. There is complete agreement that the administration of penicillin alone in early syphilis results in (1) the rapid disappearance of T. pallidum from lesions; (2) the rapid healing of skin and mucous membrane lesions; (3) the reversal to negativity of serologic reactions in more than 90% of the patients during the first two years following therapy, and (4) the completion of therapy on an ambulatory basis in the majority of patients. Another tremendous advantage of penicillin therapy is its safety, since arsenical therapy by any schedule carries a definite irreducible risk of reaction and even death. To place into effect the best ambulatory schedule for the treatment of early syphilis will require the close collaboration of investigative clinicians throughout the world. International meetings of such workers, which have been made possible by the World Health Organization, where therapeutic problems can be fully discussed, will help tremendously in solving this problem.

Gougerot and Degos [209] have also detailed their concepts of treatment of early syphilis. They divided their report into two parts. The first part is a general survey of the present views of French syphilologists on the treatment of early syphilis.

The majority of French syphilologists have adopted as "attack" treatment a course of penicillin administration in doses varying, according to the authors, from 4,000,000 to 15,000,000 units given over 6 to 20 days. However, most of them remain faithful to the combination treatment with bismuth continued for at least four years. In the absence of a valid criterion for cure, only the lapse of several years can give an adequate basis for judging the effectiveness of treatment. However, results obtained from 20 years' experience make it possible for the authors to give an almost complete guarantee of recovery to a patient who has regularly followed bismuth combination treatment for four years. Recent statistics by Degos, Vissian, and Basset concerning 2,649 subjects suffering from primosecondary syphilis, who have had regular arsenobismuth or bismuth treatment for four years and who have been kept under observation for an average of 11 years, reveal a small number of relapses (0.26%) and reinfections (0.38%). Normal results on examination of 128 samples of cerebrospinal fluid made it seem pointless to continue this examination with the other patients. However, the long-term results of penicillin therapy alone cannot yet be judged. For the moment, they prefer to give their patients, who in France readily agree to prolonged treatment, the double guarantee of the initial course of penicillin therapy followed by the bismuth combination treatment. This initial penicillin treatment has, on the one hand, the advantage of rapidly sterilizing patients with contagious lesions (epidemiological importance) and, on the other hand, that of replacing the sometimes dangerous arsenicals by a perfectly tolerated drug.

The second part of Gougerot and Degos' paper deals with the problems of penicillin therapy alone and in combination. They were as follows: the minimum active concentration in penicillin therapy; the optimum posology in penicillin treat-

208: Rein. C. R.: Problèmes que pose le traitement de la syphilis récente, Prophylax. antivén. **22**:401-416 (Oct.) 1950.

209. Gougerot. H., and Degos, R.: Le traitement de la syphilis récente, Prophylax. antivén. **22**:389-400 (Oct.) 1950.

ment; the advisability of repeated courses of penicillin; the different properties of the various penicillins and adsorption-delaying solvents; the value of oral penicillin administration; the comparative value of different treatments combining penicillin with bismuth and arsenic; the treponemicidal action of the new antibiotics; the following of patients treated with penicillin alone (duration and method); the tolerance of penicillin and, in particular, of delaying solvents (intolerance with respect to procaine; other accidents reported by Huriez); the distinction between relapse and reinfection, so as to establish comparable statistics.

Lees and Watt,[210] who studied the records of 123 men who had had early syphilis in the British Armed Forces and were treated with penicillin, conclude that observation for at least two years is essential before any claim for cure of syphilis can be made. They feel that it is essential to try to assess the final results of treatment of syphilis with penicillin alone. Menze [211] also concluded that the outstanding effectiveness of penicillin on T. pallidum facilitates its use in the therapy of early syphilis.

Penicillin Resistance in Early Syphilis.—Brena Zorrilla [212] presented a case of primary syphilis resistant to penicillin. The question of low dosage (600,000 units) of the product inducing the resistance is raised. One who has had much experience with the arsenicals and heavy metals in treatment of syphilis is amazed at how infrequently such cases occur with penicillin therapy.

Masking or Unveiling Syphilis by Penicillin Administration.—The editor of *The New England Journal of Medicine* comments [213] on the somewhat misleading title of Reekie's article, "The Danger of Penicillin Therapy of Gonorrhea," under which he calls attention again to the possibility that the treatment of gonorrhea with penicillin may increase the risk that concomitantly acquired syphilis will go unrecognized. The title unmistakably implies that it is dangerous to treat gonorrhea with penicillin. The editor feels it is unfortunate that such great emphasis is still placed on the masking of a concomitant infection. It would be more appropriate to stress the far more important feature of the value of early and adequate treatment, both for the cure of the disease against which that treatment is directed and for the prevention or cure of the concomitant infection or potential complications of that infection by even a small dose (Eagle and associates [55]). Reekie has reemphasized the importance of recognizing the symptoms that, during the early hours after an initial dose of penicillin given for gonorrhea, may call attention to the presence of an unrecognized syphilis (febrile reaction with chilly sensations and headache beginning from four to six hours after a single injection of 150,000 units of procaine penicillin). These symptoms could be inquired into when the patient returns after his first injection of penicillin.

Effect of Previous Antisyphilitic Treatment on Present Treatment.—An interesting question which needs answering is the effect of previous antisyphilitic treat-

210. Lees, R., and Watt, L.: Treatment of Syphilis with Penicillin: Review of 123 Cases Treated in H. M. Forces, Brit. J. Ven. Dis. **26**:174-176 (Dec.) 1950.

211. Menze, H.: Muss die Frühlues mit Penicillin behandelt werden? Ztschr. Haut- u. Geschlechtskr. **10**:21-26 (Jan.) 1951.

212. Brena Zorrilla, M.: Esclerosis inicial penicilino-resistente, Actas derma-sif. **42**:173-175 (Nov.) 1950.

213. Masking or Unveiling Syphilis, editorial, New England J. Med. **244**:955-956 (June 21) 1951.

ment on present therapy. Rider,[214] of the Department of Biostatistics, School of Hygiene and Public Health, Johns Hopkins University, made an examination of the cases in the files of the Central Statistical Unit (formerly in Baltimore). This failed to reveal among patients treated with crystalline penicillin G any difference between the failure rate of patients reporting a previous treatment and that of others. Among patients treated with amorphous penicillin a small difference did exist between the failure rates of patients previously treated and that of patients without such treatment.

Penicillin Treatment Schedules.—A number of schedules of therapy for early syphilis have been reported on in the last year. Among the more interesting and definitive are a few listed below:

Single Dose Method: Rangiah [215] used procaine penicillin G with 2% aluminum monostearate in treatment of venereal diseases, based upon personal observations of 72 cases of primary, 117 cases of secondary, and 59 cases of congenital syphilis. In a preliminary study, Rodriquez and his group,[216] at the Chicago Intensive Treatment Center, present clinical evidence that a one-injection schedule employing 2,400,000 units of crystalline procaine penicillin G is effective in the treatment of early syphilis. Further and more prolonged study is needed to determine the ultimate effectiveness of this procedure.

Clinical Evaluation of Four Treatment Schedules for Primary and Secondary Syphilis: Alexander, Schoch, and Mantooth [217] employed the following four schedules in the treatment of primary and secondary syphilis (all data based on 12-month observation period):

Schedule I: Calcium penicillin in oil and wax, 900,000 units; bismuth ethyl camphorate, 3 cc.; oxophenarsine hydrochloride (mapharsen®), 0.05 to 0.06 gm.: all given at one clinic visit

Schedule II: Procaine penicillin G in oil with 2% aluminum monostearate, 4 cc. (1,200,000 units): one dose

Schedule III: Procaine penicillin G in oil with 2% aluminum monostearate, 4 cc. (1,200,000 units) per week for two doses

Schedule IV: Procaine penicillin G in oil with 2% aluminum monostearate, 4 cc. (1,200,000) units per week for four doses

The failure rates for the four schedules during the first 12 months were as follows:

Schedule I: 12.3% (6.4% relapse; 5.9% reinfected)
Schedule II: 20.2% (12.8% relapse; 7.3% reinfected)
Schedule III: 13% (6.5% relapse; 6.5% reinfected)
Schedule IV: 7.5% (2.5% relapse; 6% reinfected)

214. Rider, R. V.: The Effect of Previous Antisyphilitic Treatment on Present Treatment, as Indicated by the Records from the Nation-Wide Study of Penicillin in Syphilis, Am. J. Syph. **34**:581-586 (Nov.) 1950.

215. Rangiah, P. N.: Syphilotherapy with a Single Dose of Penicillin, Indian J. Ven. Dis. **16**:134-141 (Oct.-Dec.) 1950.

216. Rodriquez, J.; Schwemlein, G. X., and Plotke, F.: One-Injection Schedule for the Treatment of Early Syphilis, Am. J. Syph. **35**:246-251 (May) 1951.

217. Alexander, L. J.; Schoch, A. G., and Mantooth, W. B.: The Treatment of Primary and Secondary Syphilis with 4 New Schedules: Preliminary Report on 500 Cases, Am. J. Syph. **34**:420-424 (Sept.) 1950.

The percentages of patients with secondary syphilis that attained seronegativity at the end of 12 months on the four schedules were as follows: Schedule I, 63.4%; Schedule II, 55.9%; Schedule III, 57.6%; Schedule IV, 78.3%.

The authors stated that the incidence of reinfection was twice as high in primary syphilis as it was in secondary syphilis. It was the opinion of the authors that Schedule II was definitely inferior to the others and should not be used. Schedule IV was definitely superior and may be as effective as any of the other good methods of treating syphilis.

Penicillin Therapy of Early Syphilis, Employing Ten Different Methods.—In treating 127 patients with early syphilis, the Robinsons [218] employed 10 different treatment schedules. They showed once again that when a treatment schedule is prolonged many patients lapse; only 18.6% of the group scheduled for 35 weekly injections of penicillin completed the prescribed course. They were convinced that carinamide did not enhance the value of penicillin, whether the penicillin was administered orally in buffered tablets, by injection in oil and wax, or in combination with procaine. Of the entire group of persons with uncomplicated early syphilis started on treatment, only 32.5% obtained a satisfactory result in that the results of blood and spinal fluid examinations were negative six months after the completion of treatment. Although there were no adverse reactions in the group treated orally with penicillin tablets on an outpatient status for 15 days, only 15.3% completed the required amount of treatment, and of these none achieved a satisfactory result.

Treatment of Early Syphilis with Penicillin in Oil and Wax.—The now outmoded penicillin G in peanut oil and wax (P. O. B.) was used by Sobel's group [219] in the treatment of 113 patients with early syphilis. They employed a treatment schedule of 300,000 units given twice a week for eight weeks. The results in primary syphilis compared favorably with those obtained with a 16-day schedule (300,000 units daily); in secondary syphilis the results were less satisfactory. The twice-a-week schedule lends itself well to ambulatory treatment, but with it 20% of the patients did not complete therapy and thereby constitute a source of new infections. Koch [220] reports a final analysis of 547 patients who were treated for early syphilis at the San Francisco City Clinic with various types of penicillin in oil and wax administered on an ambulatory basis. Four hundred eighty-one patients completed treatment. These patients received a total dose of 3,000,000 units of penicillin in an absorption-delaying vehicle. Four hundred twenty-three of these were followed for periods of less than 3 months to more than 48 months. Among the patients followed, there were 51 relapses (23 primary and 28 secondary cases). In three instances relapse occurred as late as 21 months after treatment. Failure rates are tabulated as follows: 423 cases followed 0 to 54 months, 12.1%; 359 cases followed 3 to 54 months, 14.2%; 308 cases followed 6 to 54 months, 16.6%;

218. Robinson, H. M., and Robinson, H. M., Jr.: Antibiotics in Early Syphilis and in Syphilis Complicated by Pregnancy, A. M. A. Arch. Dermat. & Syph. **63**:687-701 (June) 1951.

219. Sobel, N.; Chargin, L.; Rein, C. R., and Rosenthal, T.: The Treatment of Early Syphilis with Crystalline Penicillin G in Peanut Oil and Beeswax (P.O.B.) Employing a Treatment Schedule of 300,000 Units Given Twice a Week for a Period of 8 Weeks, J. Invest. Dermat. **15**:13-18 (July) 1950.

220. Koch, R. A.: Ambulatory Intensive Treatment of Syphilis with Penicillin in Oil and Wax: Final Report, Urol. & Cutan. Rev. **54**:534-546 (Sept.) 1950.

280 cases followed 9 to 54 months, 18.2%. There was a difference of more than 15% in the retreatment rate in patients with primary seronegative syphilis and those with secondary syphilis. The author states that the results of this study indicate that all patients treated intensively with penicillin for early syphilis should be observed for a minimum of 24 months after treatment.

Treatment of Early Syphilis with Penicillin in Oil and Aluminum Monostearate: Evaluation of Treatment Schedules.—Thomas, Rein, Landy, and Kitchen [221] report their results in the treatment of dark-field-positive early syphilis with procaine penicillin in oil with 2% aluminum monostearate. Treatment was on an ambulatory basis, and the following three schedules were employed: The first schedule consisted of a single injection of 1,200,000 units; the second of 1,200,000 units once a week for two weeks; the third of 1,200,000 units once a week for four weeks. However, the material in the three schedules is not comparable, since patients with lesions of longer duration usually received multiple injections. Of 71 patients given a single injection of either 1,200,000 or 2,400,000 units of procaine penicillin in oil with 2% aluminum monostearate and followed for 6 to 20 months, 60 (84.5%) were completely seronegative when last examined. Of 67 patients treated with 1,200,000 units once a week for two weeks and followed for 6 to 20 months, 41 (61.2%) were seronegative when last examined, and of 68 patients who received four injections, 41 (60.3%) were seronegative. On the basis of the percentages of patients who were seronegative when last examined, these statistics indicate that the single-injection treatment was superior to the treatment with two or four injections at weekly intervals. The differences in the percentage of patients who became seronegative in each of these series may be explained by the shorter duration of the infection in the patients who received a single injection. Further analysis of the material shows that 91.3% of the patients given a single injection, 83.6% of those given two injections, and 86.7% of those given four injections were seronegative or had Kahn titers of 8 or less when last examined. Statistically, the differences between 91.3 and 83.6% are not significant for series such as these; from past experience it is known that patients with low quantitative serologic titers for syphilis more than six months after treatment may be regarded as having a satisfactory status. The percentages of possible relapses after the single-, two-, and four-injection schedules are 2.9, 6, and 4.5, respectively. Considering the selection of patients and the small number of patients in each series, the differences between these percentages are insignificant. It is the impression of the authors that the long-sought-for goal of a successful single-injection treatment of early syphilis has been attained in the great majority of patients. From the data given in this report and also from the data collected by the United States Public Health Service, reported by Bauer and his associates, a single injection of 1,200,000 or 2,400,000 units of procaine penicillin in oil with 2% aluminum monostearate has given as good results in the treatment of early syphilis as injections of 1,200,000 units once a week for two or four weeks. One hundred forty-three patients were treated by Thomas and his group [222] with four schedules

221. Thomas, E. W.; Rein, C. R.; Landy, S., and Kitchen, D. K.: Results of Single and Multiple Injection Schedules for the Treatment of Early Syphilis with Penicillin in Oil and Aluminum Monostearate, Am. J. Syph. **34**:331-337 (July) 1950.

222. Kitchen, D. K.; Rein, C. R., and Thomas, E. W.: Results of Single and Multiple Injection Schedules for the Treatment of Early Syphilis with Procaine Penicillin in Oil and Aluminum Monostearate, Acta dermat.- venereol. **30**:362-371, 1950.

of injections of from 1,200,000 to 4,800,000 units of penicillin. Of these, 17 were lost from observation, and, of the remaining 126 patients, 113 either became seronegative or showed a marked serologic improvement.

Aufranc and Price [223] have compiled a composite report of the results obtained with procaine penicillin in oil containing 2% aluminum monostearate in the treatment of secondary syphilis in two series. Three schedules were employed in the first series: 1,200,000 units in one injection; 2,400,000 units in two injections (1,200,000 units seven days apart); 4,800,000 units in four injections (1,200,000 units at weekly intervals). The highest cumulative retreatment rate (32%) and the lowest rate of seronegativity occurred with the one injection of 1,200,000 units. The lowest cumulative retreatment rate (8.7%) and the highest rate of seronegativity (72.2%) occurred with 4,800,000 units in four injections (1,200,000 units at weekly intervals). Results with this schedule compare favorably with those obtained with the same amount of crystalline penicillin G in aqueous solution in doses every two or three hours. The percentage of reinfection was approximately the same for the three schedules (2.5 to 3.6%). The rate of infectious relapse was 14.5% with 1,200,000 units, 2.9% with 2,400,000 units, and 3.6% with 4,800,000 units. The second series consisted of 14 patients treated with low doses of aqueous penicillin (1,250 to 5,000 units per kilogram of body weight); 37 treated with 10,000 units per kilogram; 40 treated with 20,000 units per kilogram; 146 given 40,000 units per kilogram, and 157 patients treated with 80,000 units per kilogram. A definite pattern appears in this series, i. e., the higher the dosage, the lower the retreatment rate and the higher the seronegativity rate. It is interesting to note that in at least two patients with secondary syphilis treated by a schedule which averaged only 183,000 units of penicillin per patient the outcome was satisfactory.

Buschemeyer, Loveman, and Laugg [224] treated 102 persons having primary and secondary syphilis with procaine penicillin in oil and aluminum monostearate and followed them for 3 to 18 months. The dosage was 300,000 units once a week for four consecutive weeks (1,200,000 units of penicillin). The over-all cure rate (clinical and serologic) was 89.3%. The clinical cure rate was 94.7%. Clinical relapse occurred in 5.3%. Satisfactory serologic results were obtained in 83%; relapse occurred in 15.1% and possible reinfection in 1.9%. The authors feel their results compared favorably with those of similar series reported.

Because of the American successes, Hussels [225] treated 43 patients with procaine penicillin G in oil with aluminum monostearate (flo-cillin®) and made an 8 to 12 month follow-up study of 32 of them. Every patient received one injection of 600,000 units of the penicillin preparation a day for three days, for a total of 1,800,000 units. In seronegative primary syphilis (eight patients) he claims 100% cures (in accordance with the American experience). Those with seropositive

223. Aufranc, W. H., and Price, E. V.: The Treatment of Secondary Syphilis with Procaine Penicillin and Aluminum Monostearate: A Progress Report in Evaluation of Therapy, Am. J. Syph. **35**:57-66 (Jan.) 1951.

224. Buschemeyer, W. C.; Loveman, A. B., and Laugg, F. B.: Treatment of Early Syphilis with 4 Weekly Injections of Procaine Penicillin and Aluminum Monostearate, Am. J. Syph. **35**:67-71 (Jan.) 1951.

225. Hussels, F.: Ergebnisse über Schnellbehandlung der Syphilis mit PAM (Procain-Penicillin G in Oel mit Aluminiummonostearat) nach 8-12 Monaten Beobachtung, Therap. Gegenw. **10**:332-336, 1950.

primary and secondary syphilis (13 patients) showed no clinical relapse. Fifty per cent had serologic cure and the other 50% reduction of the titer—except for two patients. Among those with latent syphilis (four patients), two were seronegative, one showed serologic improvement, and one remained seroresistant. Moreover, the author reports a few cases of tertiary syphilis with satisfactory clinical results on rapid penicillin treatment.

Treatment of Early Syphilis with Three Injections of Penicillin and with One Injection of Penicillin.—Ninety-seven patients with dark-field-positive primary or secondary syphilis were treated by Wright and his co-workers [226] with 600,000 units of procaine penicillin G in peanut oil, containing 2% aluminum monostearate, daily for three days. The cumulative retreatment rate after more than a year of observation was 11.5%, but this included a probable reinfection rate of 8.6%. There were no clinical relapses; so the cumulative retreatment rate because of serologic failure was 2.8%. One hundred twenty-three similar patients were treated with just one injection of 600,000 units of the same penicillin preparation. At the 13th month of observation the cumulative retreatment rate was 19%, which includes 11.5% serologic failures, 5.2% clinical relapses, and 2.3% probable reinfections. Thus, the one-injection schedule is considered unsatisfactory, but the three injections are called "an effective and adaptable regimen for the ambulatory treatment of early syphilis."

Treatment of Early Syphilis with Penicillin, Arsenical, and/or Bismuth Preparations.—The value of combining penicillin therapy with arsenical and/or bismuth preparations has been known since the introduction of penicillin. In fact, as noted above, actual preparations containing penicillin and, for example, bismuth have been studied. Although there may be increased toxicity as a result of these combinations, further study is warranted. We cite a few of the recent contributions to this phase of therapy of early syphilis.

Of 744 patients with early syphilis treated by Jefferiss, Willcox, and McElligott [227] at St. Mary's Hospital, London, from 1946 to 1948, 561 received an eight-day course of penicillin, neoarsphenamine, and bismuth administration, while the remaining 183 received penicillin and bismuth only. Follow-up of 3 to 24 months or more revealed 13 known relapses. These authors are becoming convinced that, provided penicillin-resistant strains of treponemes do not appear, the end of the arsenical era is probably at hand, and that the best treatment of syphilis in the future will be effected without the aid of these drugs. On the other hand, Plotke and his colleagues,[228] who from April to August, 1946, treated 198 patients at the Chicago Intensive Treatment Center with amorphous sodium penicillin in distilled water, dichlorophenarsine hydrochloride (clorarsen®), and bismuth sub-

226. Wright, R. D.; Nicholson, F. P., and Arnold, R. C.: Treatment of Early Syphilis with Three Injections of Penicillin and with One Injection of Penicillin, J. Ven. Dis. Inform. **31**:235-240 (Sept.) 1950.

227. Jefferiss, F. J. G.; Willcox, R. R., and McElligott, G. L. M.: Treatment of Early Syphilis with Penicillin, Neoarsphenamine, and Bismuth, and with Penicillin and Bismuth Alone, Lancet **1**:83-85 (Jan. 13) 1951.

228. Plotke, F.; Rodriquez, J., and Schwemlein, G. X.: The Synergistic Action of Penicillin in Combination with Arsenic and Bismuth in Early Syphilis: A Report of 198 Patients Treated with 2.4 Million Units of Sodium Penicillin Combined with Arsenic and Bismuth, Am. J. Syph. **34**:425-430 (Sept.) 1950.

salicylate in oil for seven and one-half days, found synergistic activity of these drugs. The cumulative failure rate was 15.4% after 12 to 15 months and 20.0% after 24 to 27 months.

Danbolt and Berdal [229] report that since Jan. 1, 1947, all patients with early syphilis who have been admitted to the clinic (The Dermatological Clinic of the University, Oslo, Norway) have been given a combined penicillin-oxophenarsine-bismuth course. This includes 5,000,000 units of penicillin G in aqueous solution administered in doses of 50,000 units every three hours day and night, oxophenarsine hydrochloride in doses of 1 mg. per kilogram of body weight every day (a total of about 450 mg.), and 6 to 12 doses of bismuth in oil of 1.5 ml. twice a week. In the course of 1947 a total of 104 patients with early syphilis was treated (46 with primary syphilis, 49 with secondary syphilis, and 9 with early secondary recurrences. In a few cases the oxophenarsine administration had to be discontinued after a few injections because of slight symptoms of intolerance. Otherwise the course was administered without any particular trouble. In some cases of urticaria, an antihistaminic agent was given so that treatment could be completed. After discharge, clinical and serologic follow-up examinations have been made on 84 of the original 104 patients, with an observation period up to 25 months. Of 85 patients who were treated sufficiently long ago that the observation period could be a year or more, 69 (81%) have been followed up. Up to that time five failures, or 5.95%, were observed in 84 patients. Among the recurrences are included cases which were Wassermann-fast, cases of serologic and clinical relapse, as well as those of possible reinfections. Of the 26 patients with an observation period of 21 to 23 months, 24 were reexamined and 23 had remained symptom-free. Six failures, or 7.14%, have been demonstrated during the observation period. Control studies of the spinal fluid were carried out during the observation period on 46 patients, and the spinal fluid was normal in all cases. In five of these patients the spinal fluid showed pathological findings *before* treatment. The authors give an account of some of the more recent reports of the treatment of early syphilis with various types of penicillin courses and find that the results of the combined penicillin-oxophenarsine-bismuth course in the present follow-up study have been so satisfactory that there is reason to continue with this therapeutic method in patients who can be hospitalized. In ambulatory treatment of early syphilis the same type of treatment is recommended, substituting for aqueous penicillin, procaine penicillin in oil in a total dosage of 6,000,000 units (a daily injection of 600,000 units for 10 days). The authors are aware of the fact that a combination of penicillin with an arsenic preparation to a certain extent increases the danger of complications. But by exercising careful control during treatment so that use of the arsenic preparation can be discontinued at the slightest symptom of intolerance, this risk must be regarded as slight. It is possible that this combined therapy gives better results than penicillin alone, as also indicated by the animal experiments of Eagle and his co-workers. If this should be the case, the majority of the patients will most likely prefer to take a slight risk with a penicillin treatment combined with oxophenarsine and bismuth.

229. Danbolt, N., and Berdal, T.: Penicillin-Arsenoxide-Bismuth Treatment of Early Syphilis: Follow-up Examinations with up to 2 Years Observation Time, Acta dermat.-venereol. **30**:354-361, 1950.

Gundersen [230] followed the outcome of 91 patients with early syphilis who had received 5,000,000 units of water-soluble penicillin (50,000 units every three hours day and night for a period of 12.5 days), oxophenarsine (eight doses of 400 mg. given three times a week), and bismuth in oil (1.5 cc. twice a week intramuscularly). From the data obtained on this small group of patients the author felt this regimen was promising.

Chargin and his associates [231] treated 470 patients with early syphilis, using a treatment schedule consisting of 6,000,000 units of penicillin, 10 to 20 injections of oxophenarsine hydrochloride, and 10 injections of bismuth subsalicylate. The results of this treatment were compared with the results secured after treatment in similar cases with penicillin alone for 16 days. The satisfactory outcome in the two groups was the same. The same percentage of cases remained seropositive. Study of the rate of relapse revealed a definite difference; after the combined treatment the relapse rate was 0.85%, as compared with 3.9% with the 16-day plan. This lower rate after combined therapy must be confirmed by further study before one can definitely recommend combined therapy rather than penicillin treatment alone.

Of 360 patients with primary syphilis reported on by Jones,[232] 268 were treated with penicillin and 92 with penicillin plus oxophenarsine hydrochloride and bismuth. All the patients completed a minimum of six months of regular monthly follow-up. In the author's experience penicillin plus oxophenarsine and bismuth has proved somewhat more efficacious than penicillin alone, the penicillin in each instance being confined to one week of therapy and the bismuth and oxophenarsine, when added, requiring eight additional weekly treatments.

Pardo-Castello and Pardo [233] report the results of treatment of 91 patients with primary and secondary syphilis with a schedule consisting of 20 doses of crystalline penicillin G at the rate of 500,000 units dissolved in 3 cc. of isotonic sodium chloride solution in one daily intramuscular dose, plus 10 to 20 doses of bismuth subsalicylate, 0.13 gm. intramuscularly twice a week. Of the 91 patients, 79 became and are still seronegative; 11 are still seropositive with a falling titer, and 1 patient returned with a serologic relapse and had to be retreated. According to the authors, the low failure rate (1.2%) indicates that aqueous penicillin is as effective as, or more effective than, penicillin in absorption-delaying menstruums. The authors feel that constant hemoconcentration of penicillin is not necessary for the effective treatment of syphilis, and that the addition of bismuth subsalicylate to any schedule of treatment enhances its therapeutic value.

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230. Gundersen, H.: Penicillin-Arsenoxide-Bismuth Treatment of Early Syphilis: Follow-Up of Patients Treated in 1947 in Oslo Municipal Hospital, Acta dermat.-venereol. **30**:442-444, 1950.

231. Chargin, L.; Sobel, N., and Rosenthal, T.: Treatment of Early Syphilis with Penicillin, Mapharsen® and Bismuth (Combined Therapy), A. M. A. Arch. Dermat. & Syph. **63**:104-114 (Jan.) 1951.

232. Jones, E. H., Jr.: Observations on 360 Cases of Primary Syphilis (Treated with Penicillin Alone or with Penicillin plus Mapharsen® and Bismuth), Ohio M. J. **47**:131-133 (Feb.) 1951.

233. Pardo-Castello, V., and Pardo, O. A.: Treatment of Early Syphilis with Penicillin and Bismuth Subsalicylate: Daily Injection of 500,000 Units of Penicillin G in Sodium Chloride Solution for 20 Consecutive Days and 10 to 20 Doses of Bismuth Subsalicylate at the Rate of 2 a Week, Am. J. Syph. **34**:431-435 (Sept.) 1950.

Arsenical-Heavy-Metal Therapy of Early Syphilis.—There are still a few centers where reliance is placed on the use of the old standard treatment for early syphilis. New arsenicals are being introduced[234]; arsenical resistance is encountered, although successfully managed by penicillin,[235] and for sustained treatment bismuth compounds still have advocates, although arsenicals and penicillin are reserved by these persons for the attack treatment.[236] The real value of arsphenamine and heavy metals in treatment of early infectious syphilis was the subject of a searching investigation by Thompson and the late Dudley Smith.[237] They found 771 cases with treatment at the University of Virginia Hospital during the years 1921 through 1933. The cases were divided into two groups on the basis of amount of treatment received during the two-year period following diagnosis. The first group received less than six injections of arsphenamine and heavy metal for six weeks. The second group received six injections of arsphenamine and heavy metal for six weeks or more. The status of 304 patients at the end of two years following diagnosis showed that only 46.9% of the patients receiving less than six injections of arsphenamine were cured, whereas 70.0% of the group receiving six or more injections were cured. The 169 patients who received six or more injections of arsphenamine had a cure rate of 90.4% in the final analysis 5 to 16 years following diagnosis. Of the patients receiving less than six injections of arsphenamine, the final cure rate was only 64.6%. The study revealed that although in some cases early syphilis was cured by a small amount of therapy in others it is difficult to cure. Subsequent treatment of latent syphilis prevented the development of late clinical syphilis in many cases. The authors conclude that the present-day trend to minimize latency, and to treat syphilis with short courses, results in more infectious relapses and reinfections in early cases and may result in extension and progression into serious, late syphilis. These seem to be good reasons for continuing therapy with the modern agents which cause so few reactions and are inexpensive.

TREATMENT OF LATENT AND LATE SYPHILIS

The benign forms of late syphilis (cutaneous and hepatic) continue to react favorably to penicillin therapy.[238] Although we realize that latent syphilis poses a real problem in evaluation of the results of treatment, the following study represents a significant contribution.

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234. Fölsch, F.; Gläser, J., and Kriegk, H. J.: Klinischer Beitrag: Beurteilung des neuen Arsenobenzol-Präparates Spirotrypan, Ztschr. Haut- u. Geschlechtskr. **10**:288-292 (April 1) 1951.

235. Körber: Klinisch salvarsanresistente Syphilis und ihre Behandlung, Arch. Dermat. u. Syph. **191**:628-637, 1950.

236. Gaté, J., and Cuilleret, P.: A propos du traitement de la syphilis récente, Maroc méd. **29**:1015-1017 (Nov.) 1950. Also see previous two references.

237. Thompson, R. C., and Smith, D. C.: Evaluation of the Treatment of Early Syphilis with Arsphenamine and Heavy Metal, Am. J. Syph. **34**:410-419 (Sept.) 1950.

238. Harris, J. H., and Meltzer, L.: Generalized Late Cutaneous Syphilids: Report of a Case, Texas J. Med. **46**:845-847 (Nov.) 1950. Combes, F. C.: Tertiary Syphilis with Multiple Gummas of Skin and Bones Responding Poorly to Penicillin Therapy, A. M. A. Arch. Dermat. & Syph. **63**:138-140 (Jan.) 1951. Nicol, C. S., and Terry, R. B.: Late Syphilis of the Liver Treated with Penicillin, Brit. J. Ven. Dis. **27**:20-22 (March) 1951.

Clinical Observations on Serologic Test for Syphilis in Penicillin-Treated Early Latent Syphilis.—Thomas, Landy, and De Mello [239] report the data obtained from the histories of 127 patients with diagnoses of early latent syphilis, treated with penicillin at Bellevue Hospital, New York City, during the past five years. The diagnosis of probable early syphilis of less than three years' duration was made when the patient gave a history of a previous negative serologic reaction for syphilis within that time. None had had any previous antisyphilitic treatment, and all had negative results on cerebrospinal fluid examinations for syphilis. Treatment consisted of 3,500,000 to 4,000,000 units of penicillin given over 10 to 12 days. Some were re-treated with 4,000,000 to 12,000,000 units of penicillin because of persistently high titers on serologic tests for syphilis one or more years after the first treatment. Serologic data prior to treatment showed that 68 (53.5%) had titers of 50 or more on either the Kahn or the New York State Health Department complement-fixation test. Fifty-nine (46.5%) had titers of less than 50; 14 (11.0%) had marked discrepancies between complement-fixation and Kahn titers. One to four years after treatment 28 (22.0%) became seronegative, and 27 (21.3%) had significant drops in titer to less than 10. An additional 10 patients (8.0%) had negative reactions with one test and positive with the other. Nine patients (7.0%) had serologic relapses. Forty patients (31.5%) had drops in titer, which remained at 16 units or more one year after treatment. Thirteen patients (10.2%) had no significant changes in titer following treatment. Because the authors believed that most of the patients in this series had relatively early latent syphilis, 38 patients with titers on serologic tests for syphilis ranging between 16 and 256 units for more than one year after original therapy were re-treated. Sixteen have not been followed long enough since re-treatment for any conclusion to be reached. Nine have had no significant change in titer for 6 to 20 months after re-treatment, and five had significant drops in titer within one year after re-treatment. The authors state that they are not sure that the re-treatment was responsible for the drops in titer in the five cases. However, at present the authors advise at least one re-treatment with relatively large amounts of penicillin for patients who continue to have relatively high titers on serologic tests for syphilis more than one year after their original treatment for probable early latent syphilis.

THERAPY OF CARDIOVASCULAR SYPHILIS

There is growing acceptance of penicillin as the safe, effective base for the management of cardiovascular syphilis. Aside from the appearance of a novel way to treat aortic aneurysm (i. e., repair of aortic aneurysm with polyethylene plastic films [240]), the bulk of the literature has been a series of careful evaluations chiefly from various parts of the United States on the effect of treatment on the progress of cardiovascular syphilis and the present status of penicillin therapy.

Effects of Treatment on the Prognosis.—In a most valuable study Barnett and Small [241] present their analysis of the outcome of treatment in 334 patients with

239. Thomas, E. W.; Landy, S., and De Mello, L.: Variations of Serologic Pattern in Patients Given Penicillin Therapy for Supposed Early Latent Syphilis, Am. J. Syph. **34**:364-372 (July) 1950.

240. Cowler, H. E. S., and Sullenberger, N. H.: Successful Repair of Aortic Aneurysm with Sternal Perforation, J. Thoracic Surg. **21**:159-163 (Feb.) 1951.

241. Barnett, C. W., and Small, A. A.: The Effect of Treatment on the Prognosis of Cardiovascular Syphilis, Am. J. Syph. **34**:301-318 (July) 1950.

cardiovascular syphilis from the Stanford Syphilis Clinic, San Francisco. Only patients with aortic regurgitation or saccular aneurysm are included, so that the difficult question of the diagnosis of simple or uncomplicated aortitis may be avoided. The authors point out the difficulties and errors inherent in a comparison of two groups based upon the amount of treatment received by each group. Conventional antisyphilitic therapy in the prepenicillin days required long periods for its administration, and, with the often unpleasant and not uncommonly severe reactions associated with it, adequate treatment could be given only to patients who lived for a considerable period and whose physical status was also reasonably good. In these circumstances correlation of outcome and total treatment will inevitably give the same result. The most severely ill patients will always be in the little-treated group, and only more rugged persons with milder disease can survive to receive adequate therapy. The incidence of congestive heart failure prior to treatment is an excellent index of severity of the disease. Barnett and Small divided their 334 cases of cardiovascular syphilis into two groups, depending upon the amount of therapy received. The median amount of therapy was found to be 35 doses of arsenic or heavy metal. A few patients who received more than 1,000,000 units of penicillin were considered to have adequate treatment. When the histories were reviewed and summarized, all patients were classified in four categories of severity. The largest group was entirely asymptomatic, and those with symptoms were divided into mild, moderate, and severe. The mild symptomatic group had dyspnea or precordial pain but showed no objective evidence of myocardial insufficiency. The moderate and severe groups had physical signs of heart failure, as well as symptoms. There is a slight reduction in mortality with treatment in the asymptomatic and mild failure groups, and quite an impressive one in patients with moderate and severe failure. In the symptomatic group the duration of life from symptom onset to death is increased by about 25% in patients receiving much therapy. The mortality rate was 17% higher in the group receiving inadequate treatment. The authors conclude from the analysis of the data that treatment results in cardiovascular syphilis seem to follow a fairly definite pattern. There is consistent diminution in the effectiveness of specific treatment as the disease advances. Therapy is of doubtful value after symptoms have appeared but is definitely effective if there has also been a moderate amount of therapy before the onset. It is definitely effective when administered after cardiovascular disease has developed, but before it has advanced to the symptom-producing stage, and even more effective when given before the diagnosis has been established. If these findings are projected farther back, it might be expected that even earlier treatment would still more certainly prevent or postpone death from cardiovascular syphilis, and this is generally thought to be the case. There seems to be no point in the progress of the infection beyond which we can say that specific treatment is of no avail, but as the disease advances into the later stages of heart failure specific therapy certainly loses a great deal of its value. Penicillin is an ideal drug for the study of therapeutic effect in cardiovascular syphilis because of lack of toxicity and short time required for completion of adequate course.

Bruetsch [242] believes that the occurrence of untoward reactions when cardiovascular syphilis is treated with penicillin has been overemphasized. Penicillin may

242. Bruetsch, W. L.: Penicillin Therapy of Cardiovascular Syphilis with Large Total Dosage: Its Rationale Based on Histologic Studies, Am. J. Syph. **35**:252-254 (May) 1951. Bruetsch.[185]

be safely administered in unrestricted dosages from the start without any preparatory heavy metal treatment. From his histopathologic studies of the aorta, Bruetsch feels that because of the extreme resistance of the syphilitic exudate in cardiovascular syphilis, a total penicillin dosage of 25,000,000 units, given in the usual daily dose of 400,000 to 600,000 units, will be needed to achieve ultimate regression of the inflammatory cells from the aortic lesions. Of course, rupture in cases of far-advanced syphilitic aneurysm with paper-thin aortic wall will not be prevented by penicillin treatment.

Johnson and Shapiro [243] record their observations on the treatment of syphilis of the cardiovascular system in 17 patients. Each patient received 4,008,000 units of aqueous penicillin G according to a gradually increasing dosage schedule. Five of the 17 patients died, presumably from cardiac failure (since autopsies were not performed) at 2, 270, 350, 527, and 845 days, respectively, after treatment. Two patients having aneurysm died an average of 23 months after symptoms started, and those with aortic insufficiency, an average of 55 months. This observation would indicate that an aneurysm with symptoms carried the poorer prognosis. A review of the five cases which ended fatally to find the best procedure to follow in prognosticating the course of patients still living would indicate that the orthodiagram is much more valuable than the electrocardiogram, roentgenogram, or physical examination. Changes observed on the orthodiagram, including the appearance of early aneurysm where none had been before, increase in size of aneurysm, increase in the size of the heart and dilatation of the right subclavian artery, served as warning signs that treatment had not arrested cardiac damage.

Edeiken, Ford, and Stokes,[244] of the University of Pennsylvania, continue their observations on their increasing group of patients treated for cardiovascular syphilis with penicillin. Their latest addition was the treatment of a group of ambulatory patients with procaine penicillin, 600,000 units in a single injection daily for 10 days. There were no untoward reactions, but the desirability and effectiveness of this treatment cannot be determined until after a considerable period has elapsed. On the basis of observations made during the past six years, this group now can make certain definite statements. Penicillin can be given without fear of a severe reaction; neither therapeutic shock nor therapeutic paradox was produced in cardiovascular cases. Patients with signs of congestive failure and/or nocturnal dyspnea, angina pectoris, healed coronary occlusion, and acute myocardial infarction were treated without untoward effects. That penicillin exerts a favorable influence is suggested by (1) the change in aortic diastolic murmurs after treatment in some cases, (2) the favorable response of some patients with paroxysmal dyspnea, (3) the improvement in some cases of angina pectoris, and (4) the sense of well-being experienced by most patients.

TREATMENT OF NEUROSYPHILIS

A critical review of the literature on neurosyphilis, such as was made by Rose and Perlo,[245] indicates that penicillin has dominated the field of neurosyphilis investigation for the past five years, and that results published from many treatment

243. Johnson, S. A. M., and Shapiro, H. H.: Observations on Treatment of Cardiovascular System Syphilis with Aqueous Penicillin G, A. M. A. Arch. Dermat. & Syph. **63**:426-432 (April) 1951.

244. Edeiken, J.; Ford, W. T., and Stokes, J. H.: Observations in Penicillin-Treated Cardiovascular Syphilis, Pennsylvania M. J. **54**:229-233 (March) 1951.

245. Rose, A. S., and Perlo, V. P.: Neurosyphilis, Am. J. Psychiat. **107**:530-532 (Jan.) 1951.

centers have been remarkably similar. In spite of this, there are still die-hards, notably in France,[246] who hesitate to abandon their methods (arsenical-bismuth treatment) in favor of a new therapy until there has been a sufficient lapse of time to prove the value of such new treatment. At least 15 to 20 years are needed, since this is the average period between the appearance of the chancre and the first signs of tabes or dementia paralytica. This year's literature reaffirms the justification for the growing confidence in penicillin therapy, even to the point of conceding that penicillin alone does as much with less danger as does penicillin and fever therapy. Certainly it does more than the older therapies. Dattner [247] is still championing the cause of the superiority of the laboratory over the clinical signs as a guide to activity of neurosyphilis and to therapy. Lange and Harris [248] make a case for the diagnosis of neurosyphilis in the asymptomatic phase, thus giving precedence to laboratory over clinical signs in early diagnosis and treatment. Likewise, in follow-up study after therapy abnormalities in the cerebrospinal fluid may precede the clinical findings. The laboratory findings must be quantitative to be of definite value in early detection of progression. Case finding and case holding plus public health education are indispensable in reducing the cases of undetected neurosyphilis. The authors advise repeating the cerebrospinal fluid studies for many years if necessary, until the results are negative. Their program, therefore, consists of optimum laboratory methods and adequately controlled treatment schedules combined with effective case finding and case holding. This should reduce paresis considerably below the present incidence. As a follow-up, Dattner [249] reports the results of retreatment in three cases of asymptomatic neurosyphilis with massive doses of penicillin. All three patients had failed to respond to previous therapy with apparently adequate dosage. Failure was evidenced in all three cases by elevation of the cells in the spinal fluid. Two of the three cases appeared to have reached an inactive state following treatment with large amounts of procaine penicillin in oil with aluminum monostearate (30,000,000 units given over 30 days). The third case has not been followed long enough to evaluate the result. The following are samples of the extensive studies which were reported on during this review period:

General Discussion.—In a conference on therapy of neurosyphilis,[250] Dr. Bruce Webster opened with the statement that the treatment of syphilis of the central nervous system varies with the type of the disease. He classified neurosyphilis into the asymptomatic variety, recognized by the presence of a "positive" spinal fluid, and the symptomatic variety which falls into two general categories, namely, the inflammatory group and the degenerative group. In the inflammatory group acute syphilitic meningitis and meningovascular syphilis are the most important.

246. Baudouin, A., and Lereboullet, J.: Le traitement prophylactique et curatif de la syphilis nerveuse, Prophylax. antivén. **22**:428-442 (Oct.) 1950.

247. Dattner, B.: Problèmes que posent le diagnostic et le traitement de la neuro-syphilis, Prophylax. antivén. **22**:417-427 (Oct.) 1950. Dattner, B.; Thomas, E. W., and De Mello, L.: Criteria for the Management of Neurosyphilis, Am. J. Med. **10**:463-467 (April) 1951.

248. Lange, C., and Harris, A. H.: Role of the Laboratory in the Prevention of Irreparable Injury in Neurosyphilis, Am. J. Pub. Health **41**:168-175 (Feb.) 1951.

249. Dattner, B.: Follow-Up Report on Penicillin Failures in Neurosyphilis, Am. J. Syph. **34**:373-377 (July) 1950.

250. Conference on Therapy: Treatment of Neurosyphilis, Am. J. Med. **9**:373-382 (Sept.) 1950.

The degenerative group includes tabes, paresis, and primary optic atrophy. He states that there is considerable controversy at present among authorities on the disease concerning whether therapy should be evaluated on clinical grounds or on the basis of changes in the spinal fluid. It is important to remember that in the degenerative types of the disease antisyphilitic therapy cannot be expected to restore destroyed nerve cells. For this reason Dattner and Thomas have stressed the importance of evaluation of therapy on the basis of changes in the spinal fluid. If the cell count and spinal fluid protein are above normal, they consider the spinal fluid "active." In other words, the advocates of this view believe that if the spinal fluid cell count and protein content become and remain normal as a result of treatment, even though the quantitative Wassermann reaction and colloidal gold curve remain fixed, the process in the nervous system, regardless of its type, has been rendered "inactive" and nonprogressive, whether or not the patient has achieved any degree of clinical improvement. In such circumstances they consider further treatment useless. On the other hand, Dattner and Thomas believe that if the cell count and/or protein content of the spinal fluid do not become normal after treatment, or if, after a period of return to normal, the values again become abnormal, the patient should be retreated. Dr. Webster states that many patients show inactive spinal fluids before treatment but give evidence of clinical progression of the disease, and that both the spinal fluid changes and the clinical status must be considered in evaluating therapy. According to Webster there are two schools of thought on the treatment of neurosyphilis. One group advocates the use of penicillin alone in all forms of neurosyphilis. The other group advocates the use of penicillin alone in the asymptomatic type and in the inflammatory type of symptomatic neurosyphilis, but urges concurrent fever and penicillin treatment in the degenerative types, such as tabes, paresis, and optic atrophy. Fever therapy may consist of the standard 10 to 12 paroxysms above 102.7 F. (39.3 C.) or may be the milder course of 6 to 8 paroxysms as advocated by Solomon. There appears to be general agreement that treatment with penicillin alone exerts a profoundly favorable effect in asymptomatic syphilis of the central nervous system. In paresis, tabes dorsalis, and primary optic atrophy the results are more controversial. Although penicillin extends the life expectancy of paretics, 6 to 10% die despite treatment. About 50% show improvement, and the others remain unchanged or deteriorate. At the Syphilis Clinic of the New York Hospital the first course of treatment for all cases of neurosyphilis except primary optic atrophy consists of 4,200,000 units of penicillin given in 14 days. In cases of primary optic atrophy penicillin plus fever has been used. Dr. Webster stated that there is no question at all of the desirability of discarding tryparsamide. He also said that he was not afraid of Herxheimer reactions in neurosyphilis and that he had not observed any such reactions. He stated that there were others who held a contrary view. Dr. Walsh McDermott felt that spirochetes were necessary to produce a Herxheimer reaction, which is a reflection of the killing of spirochetes. Therefore, a Herxheimer reaction in a tabetic person involves the assumption that there are spirochetes in tabes. Dr. McDermott felt that malaria therapy should be used in patients with primary optic atrophy and in paresis regardless of its hazards. In the other types he felt that malaria, being such a debilitating and potentially dangerous treatment, should not be used unless penicillin therapy had had a fair trial first.

Penicillin Therapy of Neurosyphilis: Active Spinal Fluids Almost Routinely Made Inactive by Penicillin Treatment.—In more than six years, 438 patients with neurosyphilis and initially active spinal fluids were treated by Dattner, Thomas, and De Mello [251] with penicillin alone and followed with repeated spinal fluid examinations for 6 to 75 months. Of these, 114 had asymptomatic neurosyphilis and the remainder had clinical evidence of central nervous system syphilis.

> Because clinical improvement cannot be expected when signs and symptoms are due to irreparable damage in the central nervous system, the evaluation of treatment in our series of patients is made entirely by spinal fluid examination. . . .

Of the 438 patients, 400 achieved a satisfactory result, with an inactive spinal fluid after only one course of penicillin. The initial patients were given only 2,000,000 units of penicillin, but finally 9,000,000 units was the preferred dose. All types of penicillin were used, but the optimum schedule was 600,000 units daily of procaine penicillin in oil and aluminum monostearate for 15 days. In 38 patients the infection was not arrested by the original treatment, or there was a relapse after an initial period of inactivity. Twenty-five of these were re-treated only once, and then their spinal fluid became inactive. In the first re-treatment at least 10,000,000 units of penicillin should be used. Only six patients needed more than one re-treatment. The clinical improvement in the paretics compared favorably with that in patients formerly treated with malaria. Among 40 cases of optic atrophy further progress of amblyopia was prevented in 38. An inactive spinal fluid was one in which a cell count of more than 4 per cubic millimeter became normal and the reagin titer and abnormally high protein values dropped significantly. The new quantitative Lange colloidal gold test was used as a more sensitive indicator of abnormal globulin in the spinal fluid.

Value of Penicillin Alone.—From a study of 167 patients with neurosyphilis of all types who had been under clinical and laboratory observation for over a year, Callaway and his group at Duke University [252] conclude that "penicillin alone in a dosage of four to six million units is an effective agent in the treatment of all forms of syphilis of the central nervous system."

Ingraham, Stokes, and Gammon [253] report their observations on 603 cases of neurosyphilis followed for varying periods up to seven years after treatment with penicillin. The evaluation of penicillin treatment in this study is in terms of the over-all response of the spinal fluid tests. Included in the study were 124 cases of paresis and taboparesis, 122 of meningovascular neurosyphilis, 229 of tabes dorsalis, and 128 of asymptomatic neurosyphilis. In all types of neurosyphilis the spinal fluid response was most rapid during the first year, reached a maximum between the third and fourth years, then tended to level off. The slowest and poorest spinal fluid response was obtained in paresis and taboparesis; the greatest number of normal fluids in tabes dorsalis. By the fifth year normal or near-normal fluids may

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251. Dattner, B.; Thomas, E. W., and De Mello, L.: Results of Penicillin Therapy for Neurosyphilis at Bellevue Hospital, J. Ven. Dis. Inform. **32**:33-39 (Feb.) 1951.

252. Callaway, J. L.; Flower, A. H., Jr.; Hirschmann, V. R., and Olansky, S.: A 4-Year Study of Penicillin Treatment of Syphilis of the Central Nervous System, South. M. J. **43**:412-422 (May) 1950.

253. Ingraham, N. R., Jr.; Stokes, J. H., and Gammon, G. D.: Penicillin Alone in Neurosyphilis: Spinal Fluid Response Including a Comparison with Prepenicillin Therapy, Am. J. Syph. **34**:566-580 (Nov.) 1950.

be expected in 50% of patients with paresis and taboparesis and in 70% of those with tabes dorsalis. Spinal fluid relapse occurred after the third or fourth year in 5% of cases, almost entirely in tabes dorsalis and taboparesis. Penicillin dosage varied from a single course of 1,200,000 units of aqueous amorphous penicillin to 10,000,000 or more units of rapidly absorbed aqueous penicillin or penicillin in an absorption-delaying vehicle. Increasing the total dose beyond 5,000,000 units did not improve the results. Three hundred eighty-nine patients received one course of penicillin; 214 patients received more than one course. Repetition of the penicillin course resulted in only 3 to 5% improvement over that obtained with a single course. The greatest improvement was obtained in the first two years. The authors feel that these observations suggest that repeated courses of penicillin therapy are of little value after the initial satisfactory response. In 473 patients treated with aqueous penicillin, the spinal fluid improved steadily to the end of the third year, 63% reaching normal or near normal. One hundred twenty patients were treated with penicillin in an absorption-delaying vehicle. Forty per cent of the fluids were normal or near normal at the end of the first year; improvement in the second and third years was not as great as that with aqueous penicillin. Analysis of results in 146 patients treated in prepenicillin days indicates that the spinal fluid response from penicillin is more rapid and reaches its maximum effect a year or two earlier than that from metal chemotherapy and fever.

Rose and Carmen [254] made a follow-up study of 130 paretics at the Boston Psychopathic Hospital. The data, based on case material heavily loaded with persons having severe psychopathic symptoms, indicate to the authors that good results with penicillin therapy in paretic neurosyphilis are dependent upon prompt treatment after the beginning of symptoms. The 42% recovery obtained in this group is not good for the average series of cases, but it is surprisingly good for paretic patients with symptoms for 22 months before treatment.

Penicillin plus Fever Therapy.—There still is some division of opinion on the relative merits of penicillin alone versus its use with fever therapy of various types. Sexton [255] decries the use of penicillin alone, and Epstein and Allen,[256] as well as Malikin's group,[257] give combined therapy the advantage. On the other hand, after a long experience, Curtis and his group [258] consider penicillin alone as adequate for treatment of all types of neurosyphilis, except possibly severe paresis and primary optic atrophy. Details of some of these studies follow. We also cite without further comment a careful study by Johnwick [259] on the treatment of neurosyphilis with penicillin alone and with penicillin plus an arsenical and bismuth.

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254. Rose, A. S., and Carmen, L. R.: Clinical Follow-Up Studies on 130 Cases of Long-Standing Paretic Neurosyphilis Treated with Penicillin, Am. J. Syph. **35**:278-283 (May) 1951.

255. Sexton, G. B.: Modern Treatment of Neurosyphilis, Canad. M. A. J. **62**:43-47 (Jan.) 1950.

256. Epstein, N. N., and Allen, J. R.: Treatment of Neurosyphilis with Penicillin Combined with Artificial Fever Therapy: II. Further Observations, A. M. A. Arch. Dermat. & Syph. **63**:419-425 (April) 1951.

257. Malikin, R. Y.; Baranov, A. F., and Beirachova, L. O.: Combined Penicillin and Pyrotherapy of Nerve Syphilis (Chiefly Recent Cases), Vestnik. vener. derm. **1**:24-31, 1950.

258. Curtis, A. C.; Kruse, W. D., and Norton, D. H.: Neurosyphilis: IV. Posttreatment Evaluation 4 to 5 Years Following Penicillin and Penicillin plus Malaria, Am. J. Syph. **34**:554-565 (Nov.) 1950.

259. Johnwick, E. B.: The Treatment of Neurosyphilis: Penicillin Alone Versus Penicillin plus Arsenic and Bismuth, J. Ven. Dis. Inform. **31**:303-307 (Dec.) 1950.

Epstein and Allen [256] report on the progress of 81 patients with various forms of neurosyphilis following treatment with penicillin combined with artificial fever induced by the "blanket method." Using the Dattner-Thomas formula as a measure of activity, they found that 94.8% of the patients whose spinal fluid was active before treatment showed an inactive or less active fluid after therapy. The clinical response in patients in whom the disease was symptomatic before treatment had a tendency to parallel the changes in the spinal fluid. Epstein and Allen had the definite impression that the clinical response is better when penicillin and fever are used in combination than when penicillin alone is employed, particularly in treatment of patients with dementia paralytica, optic atrophy, and meningovascular neurosyphilis. The fever therapy in these cases was administered by means of the "blanket method," and it consisted of four or five episodes of fever with temperatures of 104 to 105 F. for five hours. Penicillin was usually given in the form of procaine penicillin in oil containing 2% aluminum monostearate; the usual dosage was 300,000 units injected intramuscularly daily except Sundays for 20 injections.

Malikin and his colleagues [257] treated a series of 67 patients with neurosyphilis by the combined administration of 5,000,000 units of penicillin and typhoid and paratyphoid vaccine intravenously, beginning with a dose of 5,000,000 to 10,000,000 and increasing to 20,000,000, 30,000,000, and 50,000,000 killed organisms. The cases must be carefully chosen, and the treatment is contraindicated in cases of hepatitis, bilirubinemia, cardiovascular diseases (coronary disease, myocarditis, aortitis), acute neurovascular syphilis with optic neuritis, nephritis, pulmonary tuberculosis, chronic malaria, anemia, the hemorrhagic diatheses, dysthyroidism, obesity, and diabetes, also in patients over 50 years of age, in pregnancy, during menstruation, in cachexia, and with acute infectious diseases. The following conclusions were reached: 1. This treatment, combined with the usual specific measures, is that of choice in dealing with relapsing and seroresistant cases of recent neurosyphilis, as well as late parenchymatous forms of tabes (hospitalization is essential). 2. It is advisable to follow the above treatment by a course of bismuth and arsphenamine, thus obtaining more stable serologic results. 3. Clinical cure is more rapid than serologic cure. The results are greatly superior to those obtained with penicillin treatment without pyretotherapy. 4. Side-effects are rare if attention is paid to the various organic functions and cases unsuitable for the treatment are rejected. 5. Small doses of the vaccine are employed, and when the rise in temperature occurs they are repeated (5,000,000 to 10,000,000 killed organisms), thus avoiding the use of large doses. 6. This treatment gives better results than does pyretotherapy combined with the usual specific treatment.

Curtis, Kruse, and Norton [258] have again analyzed the data on 430 patients followed for one to five years after a single course of treatment for neurosyphilis. Two hundred twenty-one patients (51%) were treated with penicillin alone and 209 (49%) with penicillin plus malaria. The total amount of penicillin (aqueous) given was 4,000,000 units (40,000 units every three hours for 100 injections in 12½ days) alone or combined with therapeutic tertian malaria (50 or more hours of fever). Results were the same with either type of therapy as regards clinical evaluation and ability of the patient to work. Spinal fluid results were the same except for superiority of pencillin plus malaria in a group of patients with paresis as far as reversal of the precipitation (Kahn) test reaction was concerned. This

spinal fluid reversal does not seem to be necessarily related to good clinical result. Autopsy observations confirm Gammon's earlier report that there is little histologic evidence of neurosyphilis in penicillin-treated patients. Penicillin therapy alone is adequate for all types of neurosyphilis except possibly severe paresis and primary optic atrophy.

In a study carried out by Johnwick [259] at the United States Public Health Medical Center, Hot Springs, Ark., 619 patients with positive spinal fluids, most of whom had asymptomatic neurosyphilis, were treated with 400,000 units of penicillin in peanut oil and wax once a day for 15 consecutive days. Two hundred sixty similar patients were treated with the same dosage of penicillin plus eight doses of oxophenarsine hydrochloride, 0.06 gm. each, and five doses of bismuth subsalicylate in oil, 1.5 ml. each. Of the 879 patients in the study, 65.1% were followed for 6 months; 37% for 12 months, and 22.6% for 18 months. The tests followed were the quantitative blood Kahn test, the spinal fluid cell count, and the spinal fluid total protein value. There was no evaluation of psychiatric and neurologic findings after treatment. The two groups were not equally divided, as the group receiving penicillin alone had a larger proportion of white persons, females, older persons, and persons with late syphilis whose initial spinal fluid cell count was lower. A comparison of the average quantitative blood serologic test responses in the patients who were not re-treated shows that the responses were similar after use of the two schedules. There was also no difference in the response of the cerebrospinal fluid cell count and total protein. As the two groups were not equally divided initially, the adjusted cumulative re-treatment rate for the penicillin-arsenic-bismuth group was almost three times as high for the 18-month period as that for the group given penicillin alone. The study clearly showed that nothing was gained by adding arsenic and bismuth to penicillin in the treatment of asymptomatic neurosyphilis. Owing to the bias in the selection of cases for the two groups, it appears that a high initial cerebrospinal fluid cell count carries more weight as a prognostic sign than does the duration of the syphilitic infection being treated.

Clinical Reports on Treatment of Spinal Cord Syphilis with Penicillin.—Jones, Heyman, Smith, and Wilson [260] describe the results of pencillin therapy in 19 patients with various types of spinal cord syphilis of nontabetic type. The patients included in the study ranged in age from 9 to 67 years. Twelve of them were under 45 years of age. All except two had positive serologic reactions for syphilis. The spinal fluids of all 19 patients gave positive reactions. Eighteen of the patients received aqueous penicillin every three hours for 10 to 14 days, for a total dose 4,800,000 to 6,000,000 units. One patient received 5,700,000 units of amorphous penicillin in oil and wax within 19 days. Five of the patients in this study died within two and one-half years after completion of therapy. Five other patients have been observed 6 to 15 months, while nine patients have been followed two to four years. Five patients with diffuse meningomyelitis received penicillin therapy within three months after the onset of symptoms and have obtained complete or almost complete recovery. They now have only mild residual sensory disturbances or slight weakness in the lower extremities, with normal bladder and bowel func-

260. Jones, R. W.; Heyman, A.; Smith, W. A., and Wilson, R.: Penicillin Therapy of Nontabetic Spinal Cord Syphilis, Am. J. Syph. **35**:72-78 (Jan.) 1951.

tion. Treatment was not beneficial in the three patients who had had moderate or marked motor weakness for six months to seven years. One patient had a urinary tract infection and died during treatment. There were six patients with acute transverse myelitis, none of whom obtained complete recovery. Two of them showed some improvement in motor function and also regained fair control of the bladder and anal sphincter control. Two patients showed a poor clinical response and two died. One patient with Erb's syphilitic spastic paraplegia obtained only slight improvement in motor function, while the other has shown no change. One patient with the syndrome of amyotrophic lateral sclerosis showed progressive weakness after penicillin therapy. He died two years following treatment. One patient with chronic adhesive arachnoiditis obtained relief of back pains following penicillin therapy and laminectomy. She acquired cystitis and died eight months after therapy. Of the 14 patients now living, only one has obtained a completely normal cerebrospinal fluid. The remaining 13 have normal spinal fluid cell counts and protein levels but continue to show positive reactions to spinal fluid Wassermann tests with 0.5 cc. of fluid or less. Two patients manifested febrile Herxheimer reactions within 12 to 36 hours after starting treatment. Two other patients showed progression of neurologic manifestations which may have been due to Herxheimer reaction.

Intravenous Procaine Therapy: Its Use in Tabes Dorsalis.—At the Guthrie Clinic and the Robert Packer Hospital, Sayre, Pa., Kerr and Brehm [261] gave procaine intravenously for 18 months (1947 to 1949). Of six patients who received the drug for various conditions, four had tabes dorsalis. Poor results were obtained with the use of the drug in tabes dorsalis with lightning pains.

TREATMENT OF OCULAR SYPHILIS

Although penicillin may produce unusually satisfactory results in individual cases of interstitial keratitis,[262] in general its effects are disappointing. It is, therefore, of great moment that corticotropin and cortisone have been employed in the management of the ocular manifestations of syphilis.[263] At the Alto Medical Center, Alto, Ga., nine patients who had congenital syphilitic interstitial keratitis

261. Kerr, R. M., and Brehm, W. F.: Intravenous Procaine: An Evaluation of Some of Its Uses, Postgrad. Med. **8**:444-453 (Dec.) 1950.

262. Günther, J.: Keratitis parenchymatosa in ersten Lebensmonat: Behandlung mit Penicillin, Ztschr. Haut- u. Geschlechtskr. **9**:106-111 (Aug.) 1950.

263. Fitzgerald, J. R.; Bellows, J. G.; Donegan, J. M.; Gamble, R. C.; Krause, A. C.; Mann, W. A.; Perlman, M. D., and Zekman, T. N.: Early Clinical Results of ACTH and Cortisone Treatment of Ocular Diseases, A. M. A. Arch. Ophth. **45**:320-333 (March) 1951. Scheie, H. G.; Tyner, G. S.; Buesseler, J. A., and Alfano, J. E.: Adrenocorticotropic Hormone (ACTH) and Cortisone in Ophthalmology: Report of Cases, ibid. **45**:301-316 (March) 1951. Olson, J. A.; Steffensen, E. H.; Smith, R. W.; Margulis, R. R., and Whitney, E. L.: Use of Adrenocorticotropic Hormone and Cortisone in Ocular Disease, ibid. **45**:274-300 (March) 1951. Harvey, A. M.; Howard, J. E., and Kattus, A. A.: The Effect of Adrenocorticotropic Hormone (ACTH) and Cortisone on Certain Diseases of the Eye in Which Hypersensitivity Plays a Role, Bull. Johns Hopkins Hosp. **87**:461-481 (Nov.) 1950. Geddes, A. K., and McCall, M. F.: Interstitial Keratitis Treated with Cortisone, Canad. M. A. J. **63**:601 (Dec.) 1950. Leopold, I. H.; Purnell, J. E.; Cannon, E. J.; Steinmetz, C. G., and McDonald, P. R.: Local and Systemic Cortisone in Ocular Disease, Am. J. Ophth. **34**:361-371 (March) 1951.

were treated by Simpson and his group [264] with cortisone acetate locally and 600,000 units of procaine penicillin in oil with aluminum monostearate intramuscularly daily for 12 days. The cortisone acetate was prepared in a 1:4 dilution with isotonic sodium chloride solution. Two drops were instilled in each eye every hour from 6 a. m. to 10 p. m. for 10 days. Eight of the nine patients showed a pronounced therapeutic effect from this treatment. In about 24 hours there was marked diminution of the inflammation, and quickly the exudate started to clear. One patient, whose condition previously had not improved with typhoid vaccine-fever therapy and penicillin, had almost complete clearing of the eyes with the cortisone-penicillin regimen. This treatment worked just as well after a relapse as it had before the relapse. The only patient who did not improve had corneal clouding of about 28 years' duration. The best results occurred in the early acute cases, but three late cases showed marked improvement. There was no local or systemic toxic effect from the instillation of the cortisone solution into the eyes. Because it is prepared by an outstanding authority on ophthalmology (Dr. A. C. Woods) and because it represents the best statement to the present, we quote an editorial from the *American Journal of Syphilis, Gonorrhea, and Venereal Diseases* [265]:

Recent reports clearly indicate that ACTH and cortisone given parenterally have a profound effect on the inflammatory and exudative phases of certain ocular diseases. More important, it has also been shown that cortisone administered topically, either in drops or in ointment, has an equally profound effect in inflammations of the anterior ocular segment, including some cases of interstitial keratitis. The results in interstitial keratitis are, however, not as constant as those obtained in other acute inflammations of the anterior ocular segment, for example, nongranulomatous iritis.

In cases of interstitial keratitis that respond to topical cortisone therapy, the response is often dramatic, there being marked clearing of the circumcorneal inflammation and apparent absorption of the exudates from the corneal stroma within 24 to 48 hours. In the cases which respond to treatment there appears to be a definite relationship between the amount of cortisone administered topically and the therapeutic response, so much so that in some cases the inflammatory reaction can be turned off and on by increasing and decreasing the amount of the agent administered.

Cortisone may be administered topically either in drops or in ointment. If drops are used, one should employ the ophthalmic suspension 25 mg. per cubic centimeter in which the vehicle is a buffered phosphate solution with 1:5,000 benzalkonium chloride (Zephiran) as the preservative and spreading agent. The initial dosage recommended is one drop every hour during the day, and every two hours throughout the night, increasing the interval between doses as a favorable response is obtained, but again decreasing the interval if there is any indication of the inflammatory reaction breaking through. If the ointment is used, likewise in 25 mg. per cubic centimeter concentration, it should be instilled in the lower conjunctival sac every three hours throughout the day and every six hours throughout the night. With both the drops and the ointment, the eye should be covered with an eye pad to immobilize the closed lids and so facilitate absorption.

However, the response of interstitial keratitis to cortisone therapy is irregular. In ten cases treated by McLean and Woods, dramatically favorable results were obtained in six cases, the keratitis being apparently completely controlled and clearing without the usual stage of corneal vascularization. In four cases the results were unfavorable, cortisone appearing to have no effect on the corneal clouding.

It seems probable that these conflicting results may be due to the basic pathology of interstitial keratitis and the time at which treatment is inaugurated. Interstitial keratitis begins as

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264. Simpson, W. G.; Rosenblum, B. F.; Wood, C. E., and Stammer, E. L.: Local Cortisone Acetate Therapy in Congenital Syphilic Interstitial Keratitis: A Preliminary Report, J. Ven. Dis. Inform. **32**:116-119 (May) 1951.

265. Cortisone in Interstitial Keratitis, Editorial, Am. J. Syph. **35**:88-89 (Jan.) 1951.

an infiltration of the corneal stroma with cellular and plasma exudation. This is followed by a stage of actual necrosis with vascularization and a fibroplastic reaction, ultimately producing scarring. If cortisone is used before there is actual necrosis in the cornea, a favorable result may be expected, inasmuch as this agent usually controls the inflammatory and exudative stage of ocular disease. If used after actual necrosis and secondary fibrosis have occurred, no response can be expected, since it has been clearly shown that cortisone has little or no effect in degenerative ocular disease.

The present indications are that cortisone used topically will be an extremely valuable therapeutic agent in interstitial keratitis, but treatment should be instituted early in the disease, and in sufficient amount to obtain a favorable response. With topical cortisone, no fall in the circulating eosinophiles should be expected.

TREATMENT OF SYPHILIS IN PREGNANCY

Although there still is little controversy on the value of penicillin in the treatment of syphilis in pregnancy, it is shocking to read now of what was commonplace during the arsenical era. For example, Zschunke [266] believes in treating syphilis in pregnancy, or he is even willing to treat a woman who is exposed to syphilitic infection later in pregnancy, without waiting for evidence of infection. But, in his series of cases arsenical and bismuth preparations were used with three cases of arsenical dermatitis with stillbirth resulting. Fortunately, the bulk of the material on syphilis in pregnancy deals with penicillin therapy and with little in the way of mishap. Aside from the more specific articles, which will be detailed, several general discussions of this problem should be referred to.[267]

Experience at the University of Pennsylvania and the Philadelphia General Hospital over a seven-year period with the penicillin treatment of the syphilitic pregnant woman and of infantile and late congenital syphilis is the subject of a report by Ingraham.[268] One thousand sixty-three pregnant women treated with penicillin for primary, secondary, or latent early syphilis, 80 infants under 2 years of age with congenital syphilis, and 103 patients with symptomatic or latent late congenital syphilis are analyzed. As clinical controls, 10,323 pregnancies in a comparable group of women in whom syphilis was excluded by routine methods, 302 syphilitic women untreated during pregnancy, and 594 pregnant women treated with arsenicals and bismuth are used. The analysis reveals that, in the type of material reported upon, the probability of pregnancy uncomplicated by syphilis resulting in a normal full-term living infant is about 86%. The most frequent complication is prematurity (12.75%). Stillbirth (2.6%) and neonatal death (2.2%) are of low frequency. Untreated early syphilis in an otherwise similar group of patients resulted in a dead or diseased infant in about 82% of cases and increased the possibility of neonatal death 6 times and of stillbirth at term 32 times over the normal control group.

Monacelli [269] reports that since May, 1948, a campaign has been conducted in Naples for syphilis case finding among pregnant women for treatment in such cases

266. Zschunke, E.: Prophylaxe der Lues connata, Deutsche Gesundheitswesen **5**:493-498, 1950.

267. Huse, B.; Aufranc, W. H., and Goodwin, M. S.: Congenital Syphilis, Pediatrics **6**:321-324 (Aug.) 1950. Marinkovitch, R.: The Modern Treatment of Syphilis and Gonorrhoea During Pregnancy, Med. Press **225**:29-33 (Jan. 10) 1951.

268. Ingraham, N. R., Jr.: Valeur de la pénicilline employée seule pour la prévention et le traitement de la syphilis congénitale, Prophylax. antivén. **22**:448-489 (Nov.) 1950.

269. Monacelli, M.: Prophylaxie et traitement de la syphilis prénatale, Prophylax. antivén. **22**:490-499 (Nov.) 1950.

by penicillin alone. One thousand two hundred forty-one women have so far been treated. The cases involved have been almost entirely latent, undiscovered, or inadequately treated beforehand. Case finding has shown 11% of the pregnant women examined to be suffering from syphilis. The treatment consists in administration of two injections per week, each of 4 cc. of penicillin with aluminum monostearate, for a total dose of 4,800,000 units. When there is no favorable change in the serologic curve after employing this schedule before the seventh month of pregnancy, a second treatment schedule identical with the first is administered after the seventh month. No appreciable difference has been found in the results obtained with the two different dosages: 4,800,000 and 6,000,000 units. Repetition of the treatment schedule, on the other hand, has proved useful. Penicillin has lowered the serologic titer in all cases in which there is an initial strong positivity. In cases in which the initial positivity is weaker, complete and enduring reversion to negative has been obtained in 25% of cases; in 19% the reversion to negative was not maintained; in 56% the serologic titers remained unchanged—at least during the period of observation (about three to six months and longer). It has so far been possible to observe 145 newly born infants in a complete and systematic manner. It was found that, of all newly born children with positive reaction, 5.5% still gave a serologically positive result even some time after birth. From the clinical point of view, only one case of congenital syphilis was observed with the unmistakable, classic signs. On the other hand, slight presumptive symptoms have been fairly frequent.

A study of the incidence of congenital syphilis in the offspring of 631 syphilitic pregnant women treated with penicillin led Shaffer and Courville [270] to conclude that adequate penicillin treatment given during pregnancy is nearly 100% effective in the prevention of congenital syphilis. Penicillin should be given at any time in pregnancy short of actual delivery. If it is too late to prevent infection, such treatment is effective in "curing" the condition of an infected fetus in utero. Women who have been adequately treated and have progressed to seronegativity do not need to be retreated during pregnancy, provided the serologic reaction remains continuously negative. Likewise, seroresistant patients, particularly those with seropositive late syphilis with low titer, need not be re-treated. But when there is any question of unsatisfactory response to previous therapy or of willingness to remain under close observation, it is advisable to re-treat the pregnant woman. Shaffer and Courville present convincing evidence to emphasize again the fact that positive reactions to serologic tests on cord blood are not diagnostic of congenital syphilis, especially in well-treated mothers. The babies of mothers treated late in pregnancy may show persistent but gradually decreasing titers that may require several months to become negative. These probably represent infants infected in utero but responding in a satisfactory manner to the treatment administered to the mother. Likewise, osteitis of the long bones, as demonstrated by roentgenograms in such infants, does not necessarily call for further treatment.

The Robinsons [218] treated 42 syphilitic women with 300,000 units of procaine penicillin in oil once daily for 15 days and were rewarded with 40 nonsyphilitic full-term living children. One woman was at term at the time of admission and

270. Shaffer, L. W., and Courville, C. J.: Effectiveness of Penicillin in the Prevention of Congenital Syphilis, A. M. A. Arch. Dermat. & Syph. **63**:91-103 (Jan.) 1951.

had only one injection of penicillin before being delivered of a stillborn child the next day. Their only treatment failure was a mother who completed therapy at the seventh month and was delivered of a congenitally syphilitic baby. Nine hospitalized pregnant patients were given 100,000 units of penicillin three times daily administered in buffered tablets. The children born of three of the mothers (or 33.3%) were syphilitic. In one instance in which the child was normal, the mother had an infectious relapse three months following the oral penicillin therapy for her secondary syphilis.

According to Goodwin,[271] syphilitic pregnant women need not be re-treated in every pregnancy. Treatment may be withheld if (1) the mother previously received 4.0 gm. or more of arsphenamine or its equivalent plus bismuth therapy, or at least 2,400,000 units of aqueous penicillin or its equivalent; (2) the mother shows no clinical signs of active infection, and (3) the mother is seronegative or, if still seropositive, in a low titer only. Among 587 women previously treated for syphilis and followed in 819 pregnancies during which treatment was withheld, only two syphilitic children were born. Both of the failures were due to infectious relapses in the mothers, undetected until after delivery because the two women failed to return for the necessary monthly examinations in the last months of pregnancy. In the treatment of congenital syphilis the recommended schedule employing aqueous penicillin is a total dose of 100,000 units per kilogram of body weight given in 120 injections at three-hour intervals for 15 days. Clinical trials on a small scale are now being made in several clinics with procaine penicillin given in doses of 100,000 to 300,000 units daily in single injections for from 10 to 15 days. Goodwin states that "particularly with young infants, it is important to remember that time and non-specific pediatric therapeutic measures play a major role in therapy."

Bundesen and his group [272] in Chicago treated 147 women whose disease was diagnosed as early infectious syphilis. They carefully studied the outcome of 203 pregnancies in this group. There was not one case of congenital syphilis among the 78 living infants delivered of women who were treated with 4,800,000 units of aqueous crystalline penicillin G given during seven and one-half days; one stillbirth was possibly attributable to syphilis. Another group of women were treated with 2,400,000 units of aqueous amorphous penicillin given in 15 days. They gave birth to 99 living infants, of which 97 were definitely free of syphilis; 2 infants from the same mother were syphilitic; also, 1 stillborn infant in this group was probably syphilitic. Twenty-six pregnant women with dark-field-positive lesions completed treatment as late as 1 to 50 days before delivery. Twenty-four, or 92.3%, of these pregnancies terminated in the birth of healthy infants definitely free of syphilis; no cases of congenital syphilis were found; two pregnancies, or 7.7%, terminated in stillbirths, possibly related to syphilis.

Cole and his colleagues [273] allowed 341 patients, originally treated with penicillin for primary or secondary or early latent syphilis, to go untreated through a sub-

271. Goodwin, M. S.: Status of Treatment of Syphilitic Pregnant Women and of Children Who Have Congenital Syphilis, J. Ven. Dis. Inform. **31**:178-184 (July) 1950.

272. Bundesen, H. N.; Rodriquez, J.; Aron, H. C. S., and Korman, B. F.: Outcome of Pregnancies of Women Treated with Aqueous Penicillin for Early Infectious Syphilis: Prevention of Prenatal Syphilis, Arch. Dermat. & Syph. **62**:230-236 (Aug.) 1950.

273. Cole, H. N.; Plotke, F.; Thomas, E. W., and Jenkins, K. H.: Effectiveness of Penicillin in Preventing Congenital Syphilis When Administered Prior to Pregnancy, J. Ven. Dis. Inform. **31**:201-203 (Aug.) 1950.

sequent pregnancy. Of these, 263 were not pregnant when treated, and 78 were treated during an earlier pregnancy. There was a newborn fatality rate of 49.2 per 1,000 live births, which is lower than a comparable rate for the general population. Only one infant was syphilitic because of failure of treatment administered to the mother. She was given only 1,200,000 units of penicillin and remained seropositive (40 to 80 Kahn units) during the entire pregnancy. This one case of treatment failure is an incidence of 0.4% of the 229 outcomes in which the status was definitely established. There was no difference in the results whether the patient was pregnant or not when previously treated.

Treatment of Syphilis During Pregnancy with Penicillin, Arsenical Preparation, and Bismuth.—Macfarlane[274] reports on 300 pregnant syphilitic women treated with penicillin and also with arsenic and bismuth preparations. The initial dose of 0.3 gm. of neoarsphenamine was repeated after 96 hours, and thereafter 0.45 gm. was given at seven-day intervals for nine weeks. At the same time 0.2 gm. of bismuth oxychloride was given by deep intramuscular injection once weekly for 13 weeks. Altogether, the 13-week schedule included 2.6 gm. of bismuth and 4.65 gm. of the arsenic preparation. A course of penicillin therapy was given before, during, or after the completion of the arsenobismuth part of the treatment. Irrespective of the frequency of administration and the type of preparation employed, a total of 2.4 to 3 mega units of penicillin was given to patients with seronegative primary syphilis and a dose of 4 mega units to all the others. One mega unit equals 1,000,000 units of penicillin. Since the entire course of treatment requires 13 weeks, those reporting late in pregnancy could receive only one full course of penicillin, plus a varying fraction of heavy metal, before delivery. The course of arsenic and bismuth administration in 33 of the 300 cases had to be completed after the child was born. The results were satisfactory as regards the outcome of pregnancy, even when the disease was virulent and the treatment was begun late. Penicillin given with small amounts of arsenic and bismuth will protect the fetus, but it may not fully cure the mother. A full course of arsenic, bismuth, and penicillin therapy is required to cure the mother. A positive Wassermann reaction in the first few weeks of life in an apparently healthy infant does not necessarily indicate that infection has been inherited. A negative reaction does not necessarily indicate that infection has not been inherited. Repeated serologic examinations are necessary before a conclusion can be reached.

TREATMENT OF CONGENITAL SYPHILIS

Cumulating data from various parts of the world[275] confirm the favorable impression that penicillin has created with reference to its value in the treatment of congenital syphilis. Studies of the placenta in syphilitic fetuses from mothers treated with penicillin fail to reveal spirochetes.[276] Follow-up observation indicates

274. Macfarlane, W. V.: Treatment of Syphilis During Pregnancy, Lancet **1**:1069-1070 (June 10) 1950.

275. Enkvist, O.: Penicillin Treatment of Syphilitic Infants, Acta dermat.-venereol. **30**:445-447, 1950. Seige, G.: Zur Penicillinbehandlung der Lues connata, Kinderärztl. Praxis (Sonderhft.) pp. 74-78, 1950. Shaw, N. G.: Penicillin in the Treatment of Congenital Syphilis, Illinois M. J. **98**:193-195 (Sept.) 1950. Debré, R.; Lamy, M.; Mozziconacci, P., and Labesse, J.: Early and Late Congenital Syphilis: Study of Its Treatment, Semaine Hôp. Paris **27**:1321 (April 26) 1951.

276. DeGiorgi, L.: Osservazioni anatomo istologiche sulla sifilide congenita fetale e placentare trattata con penicillina, Arch. ostet. e ginec. **55**:179-191 (May-June) 1950.

that the effects are lasting. From March, 1944, to March, 1948, at the Medical Center at St. Louis, Hanchett and Perry [277] treated 142 children having previously untreated congenital syphilis with penicillin alone. Sixty-eight were under 2 years of age; 16 were between 2 and 4 years of age, and 58 were over 4 years of age. The average total dose for infants was 300,000 units per kilogram of body weight; for children 2 to 4 years of age, 150,000 units, and for those 4 to 10 years of age, an average of 115,000 units. Patients over 11 years of age received from 2,400,000 to 8,000,000 units of penicillin. All treatments were with aqueous penicillin, first amorphous and later crystalline, given at first at three-hour and then at two-hour intervals. The giving of small initial doses of penicillin to prevent a severe Herxheimer reaction was soon abandoned as it was found to be unnecessary. Ninety-five per cent of the febrile reactions observed at the start of treatment occurred in the patients under 2 years of age. In no case was therapy permanently stopped before the prescribed amount of penicillin was given. Twenty (53%) of the patients under 6 months of age were followed for more than two years. All these became clinically and serologically negative for syphilis. Thirty-two (86.5%) of the 37 patients under 2 years of age at the time of treatment, who were followed for more than two years, also showed clinical and serologic negativity. But, of the 38 patients over 2 years of age who were followed for more than two years, only 2 became seronegative. The two clinical relapses were recurrent interstitial keratitis in children who had this disease at the start of treatment. In the group of 75 patients who were followed for over two years, there were 3 deaths; but in none was syphilis or its treatment a contributory factor. Five of the eight patients who had definite spinal fluid abnormalities at the onset of treatment had repeated lumbar punctures from six months to two years after treatment. In two of these the spinal fluid was normal; the other three showed improvement but maintained a positive reaction to the spinal fluid Kolmer test.

Treatment of Congenital Syphilis with Penicillin and Acetarsone.—Adding acetarsone (stovarsol,® spirocid®) to penicillin in the therapy of congenital syphilis is another example of gilding the lily. Yet several papers dealing with this procedure have appeared during this review period.[278]

TOXIC REACTIONS TO PENICILLIN TREATMENT

As stated in the previous review,[4] we have had the impression that toxic reactions to penicillin are on the increase. This is difficult to establish on a statistical basis since many minor and even serious reactions do not get into the literature. Gilman,[279] of the United States Navy, in a brief but pointed article reminds the practitioner of the increasing number of serious types of penicillin reactions and

277. Hanchett, L. J., and Perry, M. E.: Results of Penicillin Treatment in Congenital Syphilis, J. Ven. Dis. Inform. **31**:277-286 (Nov.) 1950.

278. Brugsch, H.: Prophylaxe und Behandlung der Lues connata, Kinderärztl. Praxis (Sonderhft.) pp. 62-63, 1950. Nyhus, G.: Follow-Up Study of 30 Cases of Lues Congenita Praecox from 2 to 19 Years After Treatment with Acetarsol, Acta pædiat. **39**:122, 1950. Ocklitz, H. W.: Die Therapie der Lues connata mit Penicillin, Spirocid und Wismut, Kinderärztl. Praxis (Sonderhft.) pp. 64-74, 1950. Stenger, K.: Die kombinierte Penicillin-Spirocidbehandlung der Lues connata, ibid., pp. 59-62, 1950.

279. Gilman, R. L.: Penicillin, an Allergic Hazard, U. S. Armed Forces M. J. **1**:1155-1156 (Oct.) 1950.

of the fact that penicillin "has failed to become the substitute for the thought and drudgery necessary to evaluate the patient's complaints." Shapiro and Berris [280] report an interesting study in this connection in which 10 patients with neurosyphilis and 1 patient with tertiary syphilis of the skin were treated with penicillin according to the following schedule: From the first to the fifth day, respectively, doses of 5,000, 10,000, 20,000, 50,000, and 100,000 units of penicillin were injected intramuscularly every three hours. From the 5th to the 14th day, patients received 100,000 units intramuscularly every three hours, and an additional 1,000,000 units of penicillin dissolved in 500 cc. of isotonic sodium chloride was administered daily intravenously. As controls, six nonsyphilitic patients were treated in a similar way. Eight of the 11 syphilitic patients had toxic reactions, all delayed in type. These reactions occurred on various days during the intravenous treatment. Symptoms were malaise, headache, nausea, chilly sensation, and temperature elevation. Two patients also had exacerbation of syphilitic symptoms. Two patients (one with pulmonary complications) died after institution of the therapy. Three of the six control patients had systemic reactions: headache, malaise, chills, and fever. In all but one patient, the onset of the reaction followed intravenous injection of penicillin by one to three hours. In all patients, including controls, reactions occurred only after intravenous administration, but it is possible that the increasing intramuscular dosage that preceded it sensitized the patients and accentuated the reactions. Another possibility is that penicillin might have a direct neurotoxic effect, as suggested by the fact that delayed reactions occurred in the control group. However, exacerbation of specific syphilitic symptoms in four syphilitic patients suggests that another mechanism was operating, separately or in combination with the above. Severity of toxic reactions contraindicates the use of combined intramuscular and intravenous administration of penicillin in the schedule described in treatment of neurosyphilis.

Intrathecal medication continues to be reported as being provocative of reactions[281]; among the reactions reported are purpura,[282] electrocardiographic changes,[283] myocardial infarction,[284] injury to the peripheral nerves,[285] rheumatoid syndrome with myalgia, arthralgia, and hemorrhagic urticarial eruptions,[286] and local hemorrhagic-necrotic cutaneous reaction.[287] The use of so-called hypoallergenic

280. Shapiro, K., and Berris, B.: Dangers of Penicillin Therapy in Syphilis of the Central Nervous System, with Special Reference to Occurrence of Delayed Reactions, Minnesota Med. **34**:141-144 (Feb.) 1951.

281. Edwards, W. M., and Kellsey, D. C.: Toxicity of Intrathecal Penicillin, U. S. Armed Forces M. J. **1**:806-811 (July) 1950.

282. Criep, L. H., and Cohen, S. G.: Purpura as a Manifestation of Penicillin Sensitivity, Ann. Int. Med. **34**:1219-1223 (May) 1951.

283. Binder, M. J.; Gunderson, H. J.; Cannon, J., and Rosove, L.: Electrocardiographic Changes Associated with Allergic Reactions to Penicillin, Am. Heart J. **40**:940-944 (Dec.) 1950.

284. Pfister, C. W., and Plice, S. G.: Acute Myocardial Infarction During a Prolonged Allergic Reaction to Penicillin, Am. Heart J. **40**:945-947 (Dec.) 1950.

285. Matson, D. D.: Early Neurolysis in the Treatment of Injury of the Peripheral Nerves Due to Faulty Injection of Antibiotics, New England J. Med. **242**:973-975 (June 22) 1950.

286. Grimmer, H.: Nebenwerkungen bei der Luesbehandlung mit Penicillin, Ztschr. Haut- u. Geschlechtskr. **9**:374-379 (Nov. 1) 1950.

287. Rubens, E.: Local Hemorrhagic-Necrotic Skin Reaction Following Penicillin: Review of Literature and Case Report, J. Pediat. **38**:630 (May) 1951.

penicillins has not been too satisfactory. Simon and Feldman [288] thought that use of the aqueous doxylamine-penicillin mixture reduced the reaction rate in 292 patients from 6.5%, obtained in a control group receiving aqueous crystalline penicillin, to 2.4%. Volini and his group [289] found penicillin O to be tolerated by a patient with syphilitic heart disease who on receiving penicillin G had displayed urticaria. However, Risman and Boger [290] performed intracutaneous skin tests on 276 persons using penicillins G and BT and on 224 persons using penicillins G and O (AT). The incidence of positive skin reactions to all three penicillins showed an increase in persons with previous exposure to penicillin G and a greater increase in those with a history of previous general reactions to penicillin G. Positive skin test reactions to all three penicillins were observed in persons who denied ever having received penicillin therapy, as well as in those who had received therapy.

Therapeutic Paradox from Penicillin Therapy in Laryngeal Syphilis.—Therapeutic paradox, while hardly a toxic reaction, should be mentioned here. Suchett-Kaye [291] reports the history of a patient with laryngeal syphilis treated with penicillin. Shortly after an intensive course of penicillin treatment of a highly infectious case of early syphilis with condylomas and "mucous patches," alarming signs of laryngeal involvement appeared. Its cause is not considered to be a local Herxheimer reaction in the larynx, but scarring and deformity, the end-result of the rapid healing of the syphilitic lesion in the epiglottis and vocal cords. These phenomena frequently occur in intensively treated visceral syphilis and lead subsequently to the so-called therapeutic paradox.

Treatment of Penicillin Reactions.—Morris [292] observed 20 cases of scrotal and rectal pellagra following routine penicillin therapy, which he believes is caused by derangement of nicotinic acid metabolism. Complete healing occurred within 12 days when 100 mg. of nicotinic acid was given three times daily. Zussman [293] reported on a patient with "an unusually severe delayed serum sickness type of penicillin reaction which resisted every known anti-histaminic."

Jarisch-Herxheimer Reaction to Penicillin.—Another fatal Jarisch-Herxheimer reaction was reported by Bush.[294] His patient, a paretic, sustained this reaction despite initiation of penicillin therapy with small doses. Because of this fatality, the author recommends a preparatory course of bismuth administration prior to initiating penicillin therapy. The patient had a history of three generalized seizures prior to treatment. He had seizures (prolonged grand mal) on the third day after the start of treatment. The seizures were accompanied with temperature elevation

288. Simon, S. W., and Feldman, M. D.: Hypoallergenic Penicillin in Oil, Arch. Dermat. & Syph. **62**:314-318 (Aug.) 1950.

289. Volini, I. F.; Shlaes, W. H., and Felsenfeld, O.: Use of Penicillin O in Patients Hypersensitive to Penicillin G, J. A. M. A. **143**:794-797 (July 1) 1950.

290. Risman, G., and Boger, W. P.: Human Skin Sensitivity to Penicillin G, BT, and O: Demonstration of Cross Sensitization, J. Allergy **21**:425-431 (Sept.) 1950.

291. Suchett-Kaye, A. I.: Therapeutic Paradox from Penicillin Therapy in Laryngeal Syphilis, Brit. J. Ven. Dis. **26**:183-184 (Dec.) 1950.

292. Morris, G. E.: Genital Dermatitis Caused by Penicillin: Its Response to Nicotinic Acid, New England J. Med. **244**:758-759 (May 17) 1951.

293. Zussman, B. M.: Allergic Reactions to Penicillin: Failure of Anti-Histaminic Therapy, Memphis M. J. **25**:110 (July) 1950. See also Ann. Allergy **8**:751-753 (Nov.-Dec.) 1950.

294. Bush, S. K.: A Fatal Herxheimer Reaction in a Case of Neurosyphilis, Am. Pract. **1**:1183-1185 (Nov.) 1950.

to 104 F. and coma. He died 24 hours later. Autopsy revealed syphilitic meningoencephalitis, hemorrhage into the white matter of the frontal and temporal lobes bilaterally, and hypostatic pneumonia.

Whorton and Denham [295] observed a 27-year-old Negro woman with gummatous syphilitic aortitis and aortic insufficiency. She died suddenly 27 hours after the beginning of penicillin therapy. Autopsy revealed, in addition to the usual histologic changes of gummatous syphilitic aortitis, a marked acute inflammatory reaction in the aortic lesion which Whorton and Denham interpreted as the histologic manifestation of a Jarisch-Herxheimer reaction.

In their study of the Herxheimer reaction in a relatively small series of patients with early infectious and latent syphilis, Putkonen and Rehtijärvi [296] obtained results disagreeing with Farmer's observation that a febrile Herxheimer reaction occurs with the same frequency and severity in seronegative primary syphilis, seropositive primary syphilis, and secondary syphilis. They found that a febrile Herxheimer reaction begins to appear in syphilis during the seronegative primary stage. It is regularly present in seropositive primary syphilis and probably most intense in the late primary or in early secondary cases. Then the reaction becomes weaker and often disappears during the late secondary phase when the latent stage is approached in which the Herxheimer reaction is practically negative. They felt that the difference between Farmer's results and theirs may be due to the fact that their initial injection of penicillin was much larger than Farmer's. In their experiments the temperature was taken every hour, but in most of Farmer's material it was recorded only every four hours. In addition, their material is from one hospital, while Farmer's was collected from 20 clinics. It is also possible that the widespread use of penicillin in the United States for treatment of various diseases may have affected his patients.

TOXIC REACTIONS NOT DUE TO PENICILLIN

A striking development which has taken place in American syphilology since the introduction of penicillin therapy is the virtual elimination of arsenical reactions. This is emphasized by the preponderance of foreign articles in this section of this presentation (cf. Stiller [297]).

Fatal Reactions to Arsenicals.—Pirilä [298] reports that from 1924 to 1948, a total of 385 patients with severe reactions to arsenicals (almost all to neoarsphenamine) were treated in the Dermato-Venereological Clinic at Helsinki. Eleven patients died, of which eight were women. Dermatitis was observed in 377, liver damage in 33, renal damage and purpura in 2 cases each, and encephalopathy and polyneuritis in 1 case each. All cases with fatal outcome showed dermatitis either alone or in combination with other reactions. The extent of treatment received averaged eight injections. In all cases in which a differential leucocyte count was made, there

295. Whorton, C. M., and Denham, S. W.: The Occurrence of the Jarisch-Herxheimer Reaction in a Patient with Gummatous Syphilitic Aortitis, Am. J. Syph. **35**:255-262 (May) 1951.

296. Putkonen, T., and Rehtijärvi, K.: The Febrile Herxheimer Reaction in Early Infectious and Latent Syphilis Treated with Penicillin, Acta dermat.-venereol. **30**:1-4, 1950.

297. Stiller, K.: Salvarsanschäden und Todesfälle nach Salvarsan, Arch. Dermat. u. Syph. **190**:423-438, 1950.

298. Pirilä, V.: Fatal Reactions to Arsenicals, Ann. med. int. Fenniae **38**:177-187, 1949.

was an eosinophilia (6 to 16%). In five cases death was due to the primary injury; in the others, to secondary complications. In one case of liver damage a histologic examination was performed, revealing a centrolobular necrosis of the liver as the cause of death.

Effect of Arsenicals on Leucocyte Count.—Cases of agranulocytosis after arsenical therapy are still being reported.[299] Penicillin and dimercaprol (BAL) administration may be of value in such cases.[299b] In view of this occurrence of agranulocytosis, the study of Proppe and Dörner [300] is interesting. They found no significant effect on the leucocytes in 100 patients who had received a neoarsphenamine injection. The blood counts were made before and 20 minutes after the injection.

Arsenical Cutaneous Reactions.—Extensive intracutaneous and epicutaneous tests were carried out by Weisenberg [301] in subjects showing arsphenamine side-effects in the course of antisyphilitic treatment. The value of these tests is limited, because subjects not treated with arsphenamine also showed positive reactions, whereas negative reactions were observed in definitely allergic patients. Intracutaneous and epicutaneous tests are both necessary, for in various side-effects either the one or the other may be reliable. In some cases the intracutaneous test may give a negative reaction and the patch test a positive one. Only in 9 of 19 cases of arsphenamine exanthem (*erythème du neuvième jour*) was the intracutaneous test reaction positive, and in only 1 was the patch test positive. Definite proof of the allergic origin can be obtained only when tests are carried out during a certain stage, i. e., in the course of the exanthem. The sensitivity to arsphenamine, so to speak, is temporarily altered. In connection with this the question is raised whether arsphenamine treatment should be continued after the occurrence of arsphenamine exanthem. The author is in favor of continuation. The majority of the patch tests carried out in cases of arsphenamine dermatitis gave positive reactions, which is suggestive of the allergic nature of this affection. Generally, continuation of arsphenamine treatment is ill-advised in these cases. Angioneurotic syndromes occurring in the course of arsphenamine treatment, though usually causing negative skin test reactions, may also be interpreted as an allergic reaction. The same holds in regard to agranulocytosis and jaundice, in which case, however, interpretation should be based not only upon the results of the skin tests but also upon the clinical course. In 1936 one of us [302] studied the status of cutaneous tests in arsenical allergy. We condemn the patch test as unreliable on every count. It not only is not useful but may actually sensitize the patient. Intracutaneous tests, we believe, are even more dangerous and uninformative.

Kurth [303] in a long dissertation reports a centrally produced sweat secretion disturbance. This was total at first and later seemed to be linked to an arsphen-

299. (*a*) Weisenberg, G.: Beitrag zur Salvarsanallergie (Exanthem des 9. Tages und Agranulozytose), Dermat. Wchnschr. **122**:711-715, 1950. (*b*) Hård, S.: Agranulocytosis in Conjunction with Neoarsphenamine Treatment, Acta dermat.-venereol. **30**:449-450, 1950.

300. Proppe, A., and Dörner, W.: Das Verhalten der Leukocyten nach einer Salvarsaninjektion, Arch. Dermat. u. Syph. **190**:358-371 (June) 1950.

301. Weisenberg, G.: Die praktische Bedeutung der intrakutanen und epikutanen Hautprüfung bei Salvarsannebenwirkungen, Arch. Dermat. u. Syph. **190**:222-260, 1950.

302. Beerman, H.: The Patch Test in the Determination of Arsphenamine Sensitization, Pennsylvania M. J. **39**:690-695 (June) 1936.

303. Kurth, W.: Über eine Schweissekretionsstörung nach Salvarsanbehandlung bei Lues, Arch. Dermat. u. Syph. **190**:25-49, 1950.

amine dermatitis. The author believes arsphenamine may affect the central sweat-regulating mechanism. Doerr [304] noted that not every person with arsphenamine dermatitis will tolerate penicillin. However, penicillin treatment takes care of secondary infection and shortens the course in these cases.

Güldner [305] believes that erythema of the ninth day is not rare, nor is it harmless. This was pointed out some time ago by Leifer.[306] From a review of the literature and his own observations, Reymann [307] suggests that ninth-day erythema is a syndrome comprising both cutaneous and various noncutaneous manifestations, including hemorrhagic encephalitis. The etiological identity of ninth-day erythema and hemorrhagic encephalitis is suggested by the following points: 1. Both clinical manifestations appear after treatment with arsenicals. 2. Both appear about nine days after the first injection. 3. Both are individual parts in syndromes having several symptoms in common, among which are acute skin eruption, fever, sore throat, and various uncharacteristic cerebral and meningeal phenomena. 4. There are fully developed cases presenting both ninth-day erythema and hemorrhagic encephalitis. Reymann observed two such cases and found seven in the literature in which hemorrhagic encephalitis was associated with an exanthem corresponding to ninth-day erythema.

Lees and Buchanan [308] report two fatal cases of arsenical encephalopathy in pregnant women and advocate a scheme of treatment for syphilis which excludes arsenical drugs in pregnancy. This consists of bismuth and penicillin.

Icterus from Arsenicals.—Unusual cases, such as that reported by Stolzer and his colleagues,[309] present rather complicated clinical situations. Their patient had postarsenical obstructive jaundice complicated by xanthomatosis and diabetes mellitus. They felt that the obstructive jaundice was probably due to allergy to arsenic. The xanthomatosis was a consequence of the obstructive jaundice. The relationship of the diabetes to the other features was not clear. Syringe-transmitted jaundice has not been noted with any degree of frequency in American syphilis clinics. Sherwood,[310] however, reports on this phenomenon in four diabetic patients. Koteen, Kane, and Rosenberg [311] studied four cases of jaundice and two cases with marked hypoalbuminemia occurring during or after malaria therapy for neurosyphilis. It is believed that these cases are probably attributable to homologous

304. Doerr, K.: Salvarsan dermatitis und Penicillin Behandlung: Ein weiterer Beitrag zu diesem Thema, Ztschr. Haut.- u. Geschlechtskr. **9**:380-382 (Nov. 1) 1950.

305. Güldner, P.: Das Erythem des 9. Tages, Arch. Dermat. u. Syph. **191**:453-456, 1950.

306. Leifer, W.: The Danger of Continued Arsenotherapy in Cases of Erythema of the Ninth Day, Am. J. M. Sc. **210**:458-462 (Oct.) 1945.

307. Reymann, F. E.: Are Ninth Day Erythema and Hemorrhagic Encephalitis in Patients Treated with Arsenicals Parts of One and the Same Syndrome? Am. J. Syph. **34**:468-475 (Sept.) 1950.

308. Lees, R., and Buchanan, J. R. G.: Arsenical Encephalopathy Occurring in the Treatment of Lues During Pregnancy, Brit. J. Ven. Dis. **24**:185-186 (Dec.) 1950.

309. Stolzer, B. L.; Miller, G.; White, W. A., and Zuckerbrod, M.: Postarsenical Obstructive Jaundice Complicated by Xanthomatosis and Diabetes Mellitus, Am. J. Med. **9**:124-132 (July) 1950.

310. Sherwood, P. M.: Outbreak of Syringe-Transmitted Hepatitis with Jaundice in Hospitalized Diabetic Patients, Ann. Int. Med. **33**:380-386 (Aug.) 1950.

311. Koteen, H.; Kane, C. A., and Rosenberg, M.: Homologous Serum Hepatitis Complicating Therapeutic Malaria for Neurosyphilis, Am. J. Syph. **35**:270-277 (May) 1951.

serum hepatitis (of viral origin) because of additional evidence of severe liver damage. Zierz,[312] on the basis of his experience with seven cases, believes that the frequently combined occurrence of hepatitis with other signs of neoarsphenamine intolerance, e. g., dermatitis, pruritus, and eosinophilia, would support the existence of a true neoarsphenamine hepatitis. He [313] treated 28 persons having neoarsphenamine hepatitis with methionine, 2 gm. per day. The toxic hepatitis reacted favorably, but allergic hepatitis was not noticeably influenced.

Arsenical Reaction: Dimercaprol.—Sands and his colleagues [314] report a case of polyneuritis due to arsenic trioxide treated with dimercaprol in which marked aggravation of neurologic signs and symptoms followed the administration of usual doses of the dimercaprol. Serial urinary arsenic and coproporphyrin studies revealed a markedly elevated urinary Type III coproporphyrin excretion and a considerably elevated erythrocyte protoporphyrin. In conclusion, studies suggested that dimercaprol therapy caused a slight increase in the urinary excretion of arsenic and coproporphyrin. According to Holley,[315] diphenhydramine (benadryl®) hydrochloride, given shortly before the injection of dimercaprol, may lessen the intensity or prevent side-effects of the dimercaprol.

NEW ANTIBIOTICS

Considerable interest in the antisyphilitic properties of the newer antibiotics has been displayed during this review period. Except for a limited study of tyrothricin and streptomycin in experimental syphilis by Bessemans and Derom,[316] no new products have been introduced. A word of caution in the use of the various newer antibiotics is necessary, as suggested by the occurrence of monilial infection during their use. Woods and his co-authors [317] report 25 cases of clinical moniliasis following the therapeutic use of penicillin, aureomycin, and chloramphenicol. In vitro studies of four strains of Candida show that these antibiotics have no stimulating or suppressing effect on the rate of growth. Suppression of bacterial flora coexisting with Candida and competing for nutrition in the same substrate is thought by these authors to be the most probable cause for monilial overgrowth and host infection. Their clinical observations do not permit conclusions regarding the importance of changes in vitamin biosynthesis or other physiopathological reactions lowering host resistance to monilial invasion. Nevertheless, vitamin B complex seems to have some therapeutic value.

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312. Zierz, P.: Gibt es einen echten Salvarsanikterus? Arch. Dermat. u. Syph. **190**:456-462, 1950.

313. Zierz, P.: Behandlung der Salvarsan-Leberschäden unter besonderer Berücksichtigung des Methionins, Arch. Dermat. u. Syph. **190**:463-477, 1950.

314. Sands, J. H.; Berris, B., and Scherer, L. R.: An Adverse Effect of BAL in a Case of Subacute Arsenical Polyneuritis with Observations on Porphyrin Metabolism, New England J. Med. **243**:558-561 (Oct. 12) 1950.

315. Holley, H. L.: The Use of Benadryl in the Prevention of Reactions to BAL, Am. J. Syph. **34**:490-492 (Sept.) 1950.

316. Bessemans, A., and Derom, R.: The Antileutic Properties of Tyrothricin and Streptomycin, Antonie van Leeuwenhoek **16**:295-298, 1950.

317. Woods, J. W.; Manning, I. H., Jr., and Patterson, C. N.: Monilial Infections Complicating the Therapeutic Use of Antibiotics, J. A. M. A. **145**:207-211 (Jan. 27) 1951.

Terramycin.—Schoch and Alexander[318] report on the oral treatment with terramycin hydrochloride of 26 patients with gonorrhea, 2 with primary syphilis, and 1 patient with granuloma inguinale. In this pilot study the authors used terramycin hydrochloride in low dosage in order to establish an effective time-dose relationship. The 26 patients with gonorrhea were given a single dose of 1 gm. Twenty-three of these patients had negative smears and cultures when they were examined 24 hours later. Three still exhibited gonococci and were re-treated with 0.5 gm. of terramycin hydrochloride every six hours for three doses. After this, smears and cultures from these three were negative in 24 hours. All 26 patients were symptom-free and well one week after completing treatment. One patient with seronegative primary and another with seropositive primary syphilis were treated with 0.5 gm. of terramycin hydrochloride by mouth three times daily for seven days. In both instances the primary lesion healed in the normal manner. Spirochetes disappeared from the lesions in 24 hours. The patient with seronegative primary syphilis had been followed for six weeks, at the end of which time she was still seronegative and showed no evidence of clinical relapse. The patient with seropositive primary syphilis had been followed for only three weeks, at the end of which time the Kahn titer had dropped from 64 to 32 units. One patient with granuloma inguinale was treated with 0.5 gm. of terramycin hydrochloride every six hours for seven days. There was healing of lesions but this was less rapid than had been noted in patients treated with streptomycin. This patient had a clinical relapse two weeks after treatment.

The Robinsons[218] treated five patients suffering from early dark-field-positive syphilis with terramycin. The dosage schedule employed was 3 gm. of terramycin followed by 0.5 gm. every four hours for 15 days. They noted that the dark-field examinations gave negative results in 24 hours in four cases and in 32 hours in the fifth case. The moist genital lesions were completely healed in 7 to 12 days. There were no adverse reactions to the drug. One patient was seronegative at the first visit and remained so. There has not been sufficient time to study the post-treatment serologic reactions, and further studies must be carried out to determine the value of terramycin in syphilotherapy.

Aureomycin Treatment of Early Syphilis.—The Robinsons[218] observed 20 patients with dark-field-positive lesions of early syphilis who were treated with aureomycin either by mouth or by the intravenous method. The following dosage schedules were used: (1) 100 mg. of aureomycin administered intravenously once daily for 15 days; (2) 200 mg. of aureomycin given intravenously once daily for 15 days; (3) 1 gm. of aureomycin taken by mouth, followed by two oral doses of 0.5 gm. at four-hour intervals; this was repeated daily for 15 days; (4) 3 gm. in a single oral dose, followed by 0.5 gm. orally every four hours for 15 days. They found that aureomycin administered by the oral or the intravenous route will cause a disappearance of surface T. pallidum in 18 to 72 hours. The lesions of early syphilis heal in 7 to 14 days when aureomycin is administered by either route. The serologic titer diminishes after therapy, but further observation is necessary. No adverse reactions were noted in the group of patients treated intravenously, but

318. Schoch, A. G., and Alexander, L. J.: Terramycin in the Control of Venereal Diseases, Ann. New York Acad. Sc. **53**:459, 1950.

two of the patients treated orally had severe nausea and vomiting, and two had nausea only. No reactions were noted when recrystallized aureomycin was used.

Olansky, Hogan, Taggart, Landman, and Robin [319] report in a preliminary fashion the results of treatment of 108 syphilitic patients with aureomycin. The dosage varied from 30 to 240 mg. per kilogram of body weight a day. The duration of treatment varied from one to eight days. Since the disappearance time of organisms from the lesions was almost as short with the lower dosages as with the higher, most patients were treated with 30 to 60 mg. per kilogram of body weight a day for four to eight days. The average time for disappearance of T. pallidum from lesions was 27 hours. Primary and secondary lesions healed quickly, as rapidly as has been noted during penicillin treatment. Treatment failed in all patients who were treated for only one day. The highest percentage of seronegativity was achieved by patients treated with 60 mg. per kilogram of body weight a day for eight days. Four patients with benign late syphilis were treated. A nodular syphilid of the arm and shoulder was completely healed after administration of 3 gm. of aureomycin daily for four days. A nodular ulcerative lesion of the breast, treated with 3 gm. of aureomycin daily for eight days, was healed by the fifth day. Two gummata of the leg, one of three months' duration and the other of one year's duration and complicated by osteomyelitis, healed in 8 and 14 days, respectively. Herxheimer reactions occurred in only five cases; two patients had temperature elevation, and three showed a cutaneous flare of their secondary lesions. Two patients exhibited severe avitaminosis while receiving treatment or shortly after completion of treatment. The authors feel that aureomycin may prove to be a valuable agent in the treatment of central nervous system syphilis and cardiovascular syphilis because of the milder and less frequent occurrences of Herxheimer reactions. They feel that it may also be used in patients sensitive to penicillin.

Rodriquez and his co-workers [320] continued their study, which was previously reported,[321] of early syphilis after treatment with aureomycin. After a six or seven months' observation period, the cumulative percentages of treatment results for 62 patients with secondary syphilis were as follows: 59.7%, seronegativity; 21.1%, 3 Kahn units or below; 15.8%, 4 Kahn units or over; 1.7%, reinfection, and 1.7%, relapse. As in their preliminary report, they note that aureomycin rids the syphilitic lesions of spirochetes in an average of 39 hours. High and sustained blood levels were easily maintained by the oral route, even though most of the patients had a mild to moderate degree of gastrointestinal disturbance because of the high dose employed (70 gm. of aureomycin orally in 11⅓ days).

Aureomycin in the Treatment of Neurosyphilis.—Kierland and O'Leary [322] have treated 12 patients who had various types of neurosyphilis with aureomycin in total

319. Olansky, S.; Hogan, R. B.; Taggart, S. R.; Landman, G. S., and Robin, E. D.: Treatment of Syphilis with Aureomycin, Am. J. Syph. **34**:436-442 (Sept.) 1950.

320. Rodriquez, J.; Plotke, F.; Weinstein, S., and Harris, W. W.: Aureomycin and Its Effect in Early Syphilis: Progress Report, A. M. A. Arch. Dermat. & Syph. **63**:433-439 (April) 1951.

321. Rodriquez, J.; Plotke, F.; Weinstein, S., and Harris, W. W.: Aureomycin and Its Effects in Early Stages of Syphilis, J. A. M. A. **141**:771-772 (Nov. 12) 1949.

322. Kierland, R. R., and O'Leary, P. A.: Oral Treatment of Neurosyphilis with Aureomycin, Am. J. Syph. **34**:443-452 (Sept.) 1950.

doses ranging from 50 to 90.5 gm. Three other patients also were treated but because of various factors were unable to complete a course of treatment. Sixty grams of aureomycin, given in divided doses of 2 to 4 gm. daily, was considered sufficient for a first course of therapy. Reactions involving the gastrointestinal system and consisting of nausea and anorexia, and less frequently of vomiting and diarrhea, appeared in approximately 50% of the cases. In only 2 of the total 15 cases was it necessary to discontinue use of the antibiotics because of these reactions. Reactions of photosensitivity appeared in two cases and persisted for a month after the treatment was completed. In all but 1 of the 12 cases there was satisfactory and rapid clinical improvement. In one case of advanced paresis there was continued mental deterioration in spite of treatment, even though the spinal fluid showed continuous improvement. In all but one case rapid and great improvement was noted on examination of the cerebrospinal fluid, particularly in the cell count and values for protein. The colloidal gold reaction and complement-fixation reaction responded more slowly. The response of the spinal fluid of patients treated with aureomycin showed essentially the same pattern as that of patients treated with penicillin. The authors conclude that the early results achieved with aureomycin therapy are equivalent to those achieved from use of penicillin, and administration of aureomycin by mouth is indicated for those patients with neurosyphilis who have a resistance to, or a hypersensitivity to, pencillin.

Effect of Aureomycin on Venous Clotting Time.—Blodgett and Schilling [323] found no significant alteration of the coagulability of the blood in normal human subjects as measured by a modification of the Lee-White method.

Effect of Chloramphenicol in Experimental Rabbit Syphilis.—Gruhzit and Fisken [324] found that chloramphenicol, 50 to 75 mg. per kilogram of body weight a day in two divided doses for two and five days, did not retard or otherwise influence development of syphilitic lesions in rabbits when given by the intramuscular route. Larger amounts of chloramphenicol (100 to 200 mg. per kilogram a day in two equal doses a day for two and four days) in early progressing syphilis of rabbits (seven weeks) caused marked initial healing of lesions and temporary disappearance of spirochetes, followed by recurrence of lesions or development of syphilomas in lymph-node-transfer rabbits. Prolongation of treatment from four to eight days (200 mg. per kilogram of body weight a day, and a total of 1,600 mg. per kilogram) resulted in a satisfactory curative effect in syphilitic rabbits (100%) with long-standing infections of six to nine months' duration. The blood serum concentration in rabbits is relatively low in comparison to that in human subjects. This fact may account for the divergence of therapeutic effectiveness in the two species.

Chloramphenicol for Early Syphilis.—The Robinsons [218] observed 14 patients with dark-field-positive lesions of early syphilis, after having treated them with chloramphenicol. Their usual schedule of treatment (used in 11 patients) consisted of an initial dose of 3 gm. of chloramphenicol, followed by 0.5 gm. every four hours to a total of 48 gm. (15 days). The results of dark-field examinations were nega-

323. Blodgett, W. A., and Schilling, F. J.: The Effect of Aureomycin on Venous Clotting Time, Am. J. M. Sc. **221**:688-690 (June) 1951.

324. Gruhzit, O. M., and Fisken, R. H.: Chloramphenicol (Chloromycetin) in Experimental Syphilis of Rabbits, Am. J. Syph. **34**:338-341 (July) 1950.

tive in 24 hours in all but one case, in which they became negative in 48 hours. Rapid healing of all lesions was noted. Two men with chancres were seronegative at the start of treatment and remained so. One of the group was a seven and a half months' pregnant Negro woman with condylomata lata; she was delivered of a full-term nonsyphilitic child. Another pregnant woman with condylomata lata gave birth to a normal child, but the mother later suffered a serorelapse. Reversal of the serologic reaction to negative was observed in 70% of the cases. In a five- to six-month follow-up study, Romansky and his co-workers [325] found chloramphenicol an effective oral antisyphilitic agent. A dosage of 60 mg. per kilogram of body weight a day for six to eight days appears to give the most favorable results among the various treatment schedules followed. For neurosyphilis it is advisable to prolong therapy for at least 15 days.

Fatal Case of Aplastic Anemia Following Chloramphenicol Therapy.—Rich and his colleagues [326] report a fatal case of aplastic anemia following the prolonged use of chloramphenicol. They call attention to the fact that in 1949 Smadel stated that the presence of the nitrobenzene radical in the structure of chloramphenicol might make that drug toxic for the hematopoietic system. They were able to find one other report in the literature that indicated that chloramphenicol was responsible for marrow hypoplasia, more marked in the granulocyte series but also involving a maturation arrest of erythroid elements. The authors feel that the occurrence of such reaction makes advisable repeated blood counts on patients who receive chloramphenicol for long periods.

SYPHILOID DISEASES

World Health and Treponematoses.—Guthe and Reynolds [327] in an important presentation state that the introduction of pencillin in syphilotherapy may have contributed to the rapidity with which syphilis was brought under control in certain European countries, North America, and elsewhere, after the second, as compared with the first, World War. From a global viewpoint, the achievements in syphilis control during the last few years in certain European countries, North America, Australia, and other areas are of a limited value, since large reservoirs of syphilis and extravenereally acquired forms of other treponemal diseases remain in temperate, semitropical, and tropical areas throughout the world. The broadest possible view of treponemal diseases is called for, since millions of persons are incapacitated by "endemic" and other syphilitic diseases—bejel, yaws, and pinta—in different parts of the world where these are of economic consequence, and since the common vulnerability of T. pallidum, T. pertenue, and Treponema carateum to penicillin has demonstrated the applicability of repository penicillin preparations in the control of treponemal diseases. In the absence of important evidence of penicillin resistance in the treponemes, the introduction of procaine penicillin G in oil with 2% aluminum monostearate, which is capable of maintaining an effective blood

325. Romansky, M. J.; Olansky, S.; Taggart, S. R.; Landman, G. S., and Robin, E. D.: Chloromycetin (Chloramphenicol) in the Treatment of Various Types of Syphilis: A Preliminary Follow-Up, Am. J. Syph. **35**:234-239 (May) 1951.

326. Rich, M. L.; Ritterhoff, R. J., and Hoffmann, R. J.: A Fatal Case of Aplastic Anemia Following Chloramphenicol (Chloromycetin) Therapy, Ann. Int. Med. **33**:1459-1467 (Dec.) 1950.

327. Guthe, T., and Reynolds, F.: World Health and Treponematoses, Brit. J. Ven. Dis. **27**:1-19 (March) 1951.

level over several days with appropriate "one-shot" or "few-shot" treatment, has made a convenient, safe, and inexpensive therapy available for individual and mass control of treponemal disease. The study of the fundamental biologic and immunological relationships among the treponemal diseases should be encouraged. The reduction of reservoirs of treponemal infection to a relatively low incidence appears, fundamentally, to be attainable through two different mechanisms: one, the general socioeconomic evolution over a long period during which general health services are developed, with some accent on specific disease programs as required, and the other, the mass effort, which can be superimposed on the first at any stage, depending on the magnitude of the problem. The complete elimination of reservoirs of syphilis infection has been demonstrated in limited areas in communities in Bosnia (Yugoslavia), and that of yaws in Pacific islands and African villages. Mass campaigns against syphilis and yaws covering areas with several million persons (Bosnia, Indonesia, Thailand, Haiti) show encouraging results. However, the lasting value of such campaigns, after the initial effort, depends on the establishment of permanent treatment facilities and on other secondary measures. National health administrations may request technical and financial assistance from such international bodies as the World Health Organization and the United Nations International Children's Emergency Fund for campaigns against venereal disease and treponematoses and other health programs. Organizations are cooperating with health administrations in several countries in certain projects. Statistics are presented in Foreign Letters of *The Journal of the American Medical Association*[328] on the incidence of yaws and pinta among white, Negro, and Indian inhabitants of various regions of Ecuador. The cause, spread, and control of these diseases are discussed along conventional lines.

Effect of Orally Administered Aureomycin on T. Pertenue in Man.—Schaeffer and his colleagues[329] studied the morphologic changes in T. pertenue, obtained from primary and secondary lesions of 20 patients treated with aureomycin for yaws and observed with the phase-contrast microscope, and compared them with the appearances of normal treponemes removed from the same or similar lesions prior to therapy. In view of the easily demonstrable changes and the easily visible reduction in their numbers, the authors now use the phase-contrast microscope routinely in evaluating substances used in the treatment of yaws.

Aureomycin in the Treatment of Yaws.—Loughlin and his co-workers,[330] in a study begun in January, 1950, at the Hôpital Général, Port-au-Prince, Haiti, treated 30 West Indians who had yaws in various stages with 10 gm. of aureomycin administered orally. The authors feel that gratifying results obtained with this treatment suggest that if a comparable dose of the drug could be administered intramuscularly in a repository form, a more efficient therapy for the mass treatment of yaws might be achieved. Five children, 3 to 8 years of age, with florid secondary yaws were treated by Ampofo and Findlay[331] with aureomycin hydro-

328. Pinta and Yaws in Ecuador, Foreign Letters, J. A. M. A. **145**:922 (March 24) 1951.

329. Schaeffer, K.; Loughlin, E. H., and Joseph, A.: The Effect of Orally Administered Aureomycin on Treponema Pertenue in Man, Am. J. Trop. Med. **31**:24-25, (Jan.) 1951.

330. Loughlin, E. H.; Joseph, A., and Schaeffer, K.: Aureomycin in the Treatment of Yaws, Am. J. Trop. Med. **31**:20-23 (Jan.) 1951.

331. Ampofo, O., and Findlay, G. M.: Treatment of Yaws by Aureomycin, Tr. Roy. Soc. Trop. Med. & Hyg. **44**:311 (Dec.) 1950.

chloride. This was given in the form of capsules by mouth, 250 mg. three times daily for seven days. This dose cleared up the secondary lesions and prevented recurrence for at least six months. Aureomycin given by mouth proved also of value in two children, 8 and 10 years of age, respectively, with late secondary or early tertiary yaws. They were given 500 mg. three times daily for seven days. It appears that in patients with late secondary and in tertiary yaws aureomycin in the dosage given is less spectacular in its action than in patients with a florid secondary skin eruption. Nevertheless, it is of significant value in healing chronic ulcers and in relieving the pain in yaws periostitis. The oral administration of aureomycin caused no toxic symptoms, such as fever, headache, nausea, vomiting, or skin eruptions. Aureomycin behaves in yaws much in the same way as does penicillin. It has the advantage over penicillin in that it is effective by mouth in comparatively small doses. In mass treatment this is obviously a great advantage, since, besides the pain of daily intramuscular injections, there is a great saving of labor, apparatus, and time. It seems hardly necessary to give oral therapy for yaws when repository penicillin gives such a convenient and effective means of combating the disease, as was well demonstrated by Rein, Kitchen, and Petrus.[332]

Chloramphenicol in Yaws and Tropical Ulcer.—Ampofo and Findlay [333] also present evidence indicating that chloramphenicol shares with penicillin and aureomycin the power to heal rapidly the primary and secondary lesions of yaws and also to eliminate the bacterial flora from tropical (phagedenic) ulcers, which allows healing to take place. Like aureomycin, chloramphenicol has the advantage over penicillin that it can be given by mouth. From the small number of patients so far treated with aureomycin and chloramphenicol, it is impossible to determine which of the two is the more effective, as both antibiotics are so excellent. Payne and Bellerive [334] also report favorable results in 86 patients with yaws and tropical ulcer who were treated with chloramphenicol.

Treatment of Yaws with Terramycin.—Loughlin and Joseph [335] found that a total of 7 gm. of terramycin administered in a three-day period gave good results in 150 patients with yaws. The relapse rate was considerably less than in patients treated with 300,000 units of procaine penicillin, and the incidence of relapse with smaller dosages of terramycin was no greater than in those treated with massive doses of penicillin.

CONTROL OF SYPHILIS

One of the outstanding contributions by workers in syphilology is the definition of the present status of syphilis as a continuing disease problem. In this connection two papers deserve mention. One by Clark [336] asks whether venereal disease is

332. Rein, C. R.; Kitchen, D. K., and Petrus, E. A.: Repository Penicillin Therapy in Yaws in the Haitian Peasant: A Clinical and Serologic Survey, J. Invest. Dermat. **14**:239-246 (April) 1950.

333. Ampofo, O., and Findlay, G. M.: Chloramphenicol in Treatment of Yaws and Tropical Ulcer, Tr. Roy. Soc. Trop. Med. & Hyg. **44**:315 (Dec.) 1950.

334. Payne, E. H.; Bellerive, A., and Jean, L.: Chloromycetin as a Treatment for Yaws and Tropical Ulcer, Antibiotics & Chemotherapy **1**:88-91 (April) 1951.

335. Loughlin, E. H., and Joseph, A. A.: Terramycin in the Treatment of Yaws, Antibiotics & Chemotherapy **1**:76-87 (April) 1951.

336. Clark, G. E.: Is Venereal Disease No Longer a Problem? Am. J. Syph. **34**:401-404 (Sept.) 1950.

any longer a problem, and the other by Aufranc[337] queries whether venereal diseases are disappearing. Moore,[338] in a paper which must be seen in the original to be appreciated properly, evaluates public health measures for the control of syphilis. Since the editors of *The Journal of the American Medical Association* have analyzed Moore's studies so critically, we quote their presentation.[339]

The statement is heard with increasing frequency that syphilis is a vanishing disease. Many feel that penicillin therapy plus a continued nationwide program of case finding and education will soon relegate syphilis to the minor status of smallpox, typhoid and diphtheria. Others adopt a more conservative attitude. In a penetrating analysis, Moore points out that the long term trends in the incidence of syphilis have not been altered dramatically by antibiotic therapy and that the ultimate goal of eradication may be more distant than the optimistic would have us believe.

Available data indicate that there has been a steady decrease in the incidence of syphilis in Europe and the United States for almost a century and that this decline has been interrupted only by temporary increases in morbidity during wars or periods of civil unrest. Two observations provide clues as to the mechanism of this decline: 1. It began long before the discovery of specific therapy for syphilis or the institution of public health measures for its control. 2. It has been accompanied by a progressive decrease in the acuteness of the disease, so that an infection that was often rapidly fatal in the 15th century has evolved into one of great chronicity. These observations suggest that a gradual process of adaptation has led to a decrease in the virulence of the parasite or an increase in the resistance of the host. In addition, there is evidence that the progressive improvement in socioeconomic conditions in Western civilization has contributed to the reduction in the incidence of syphilis. Whatever the mechanisms responsible for the decrease in morbidity before the days of specific therapy, it may be assumed that they are still operative and that they may be at least partially responsible for the continued decline.

Since the introduction of specific arsenical therapy in 1910, the rate of decline seems to have been accelerated somewhat. It is difficult to make precise statements because of the incompleteness of the available data and the tendency of the periodic fluctuations in the incidence of syphilis to obscure the long-range trends. It is even more difficult to evaluate the effect of a relatively new drug such as penicillin on the curve of incidence, since the total duration of penicillin therapy has not yet exceeded one of the naturally recurring cycles of increase and decrease in the incidence of the disease. It is tempting to attribute the sharp decrease in the attack rate in the past three or four years to the widespread use of penicillin, but the fact cannot be ignored that a decline at exactly the same rate occurred after World War I, before the discovery of penicillin. At least another decade of experience with penicillin will be required before its effect on the incidence of syphilis can be measured accurately. Its value in the control of the individual case of syphilis remains unchallenged, however. It is to date the drug of choice in this disease—effective, rapidly acting, nontoxic, and inexpensive.

A factor of equal or greater importance in the accelerated decline in the incidence of syphilis has been the application of modern public health measures to the control of venereal disease. Public health authorities in this country and in Europe have accomplished a prodigious task in finding and treating millions of infected persons and in educating the public. Their efforts are reflected in the continuing decrease in the infant and adult morbidity and mortality from syphilis.

According to Moore, however, the present rate of decline is not yet sufficiently significant (except possibly in Scandinavia) to promise eventual complete control in any country, to permit a relaxation of control efforts or to set a time limit on the achievement of the desired goal. In this country in 1949, there were still an estimated 3,000,000 persons with serologic evidence of infection with syphilis, and an additional 150,000 persons acquired the infection in that year. Fourteen thousand syphilitic infants were born and 13,000 persons died of syphilis in the same

337. Aufranc, W. H.: Are Venereal Diseases Disappearing? Over-All Picture Throughout the Country, Am. J. Syph. **35**:135-137 (March) 1951.

338. Moore, J. E.: An Evaluation of Public Health Measures for the Control of Syphilis, Am. J. Syph. **35**:101-134 (March) 1951.

339. Syphilis Control, editorial, J. A. M. A. **146**:1031-1032 (July 14) 1951.

year. Six thousand persons were sent to mental institutions because of syphilis. These figures continue to decrease, but past experience has shown that eradication of a disease in one country is not enough. The continual population exchanges permitted by modern transportation make new epidemics possible as long as an endemic focus remains anywhere in the world. Densely populated China and India have a high incidence of syphilis, and these countries constitute a potential public health danger.

Moreover, as Moore points out, no infectious disease in the history of medicine has been eradicated or even partially controlled by the sole process of treatment of infected persons. Immunization may be the ultimate goal of public health control, but this in turn awaits further research on the problem of cultivation of the Treponema pallidum. Both public and private laboratories are doing their utmost to solve this problem, but financial support is needed. In the long run this type of approach is the most economical one, because global control by present methods is a practical impossibility.

Other summary statements in the current literature on the status of venereal disease control also indicate that, in spite of decrease in rates, there still remain areas with poor syphilis control,[340] and much remains to be done in the United States and Canada,[341] as well as on a world-wide scale.[342]

Syphilis in Foreign Countries.—Although Tottie[343] concludes that syphilis is still a disagreeable reality in Sweden, he does not feel that there are reliable statistics dealing with this morbid state. Likewise, in discussion on Tottie's report, Gjessing states that to date there are no investigations or statistical material which allow accurate calculation of the syphilis frequency for Norway.

In a letter in the Foreign Letters section of *The Journal of the American Medical Association,*[344] it is stated that by 1918 figures in Denmark were more accurate than for previous years. In 1919 there were 4,307 notifications of acquired syphilis. By 1938 this figure was reduced to 470. There was a decline in the incidence of gonorrhea, with 14,507 cases reported in 1919 and only 7,803 in 1940. After return of Danish soldiers from Germany in 1944, the incidence of syphilis was nine times the incidence in 1938 and the incidence of gonorrhea three times that in 1938.

In a well-written article, Willcox[345] reports on a venereal disease survey made in 1949 of Southern Rhodesia, Union of South Africa, Egypt, Turkey, Syria, Lebanon, Pakistan, and Iraq. He was impressed by the importance of syphilis as a nonvenereal complaint, and by the fact that the facilities for the treatment of syphilis are much simpler and more effective than the facilities for its diagnosis. Yaws and pinta are considered by most authorities, except Hudson, to be caused by a spirochete distinct from T. pallidum. However, other diseases of an "intermediate nature" are probably true nonvenereal syphilis. They are bejel, which

340. The Status of Venereal Disease Control, Editorials, Am. J. Pub. Health **40**:864-866 (July) 1950. Report of the Committee on Venereal Disease Control, Illinois M. J. **98**:61-63 (July) 1950. Congenital Syphilis Down 85 Per Cent, Chicago M. Soc. Bull. **53**:65 (July 29) 1950.

341. Ingraham, N. R., Jr.: Newer Developments in Venereal Disease Control in the United States and Canada, Tr. & Stud. Coll. Physicians Philadelphia **19**:25-32 (April) 1951.

342. Guthe, T.: Lutte contre les tréponèmatoses dans le cadre de L'O. M. S., Prophylax. antivén. **22**:384-388 (Oct.) 1950.

343. Tottie, M.: Morbidity of Syphilis in Sweden, Acta dermat.-venereol. **30**:513-515, 1950.

344. Venereal Diseases (Denmark), 1900-1948, Foreign Letters, J. A. M. A. **143**:1015 (July 15) 1950.

345. Willcox, R. R.: The Treatment of Syphilis of the Masses, J. Ven. Dis. Inform. **31**:254-260 (Oct.) 1950.

affects about a million persons in Iraq, and njovera, which is widespread in Southern Rhodesia. Extravenereal syphilis is commonest where there are poverty, filth, and overcrowding. The most effective and simple mass treatment of syphilis is the single injection of 2,400,000 units of procaine penicillin with 2% aluminum monostearate. Among primitive people the penile sore is most troublesome diagnostically, as dark-field facilities are not available, nor are trained technicians to use them. Therefore, in the mass treatment of primary syphilis with procaine penicillin with 2% aluminum monostearate, many patients with chancroid alone or combined with syphilis would be handled just like those with syphilis alone. This need cause no concern, however, because one dose of procaine penicillin with 2% aluminum monostearate will cure the majority of cases of chancroid. Willcox found it much more effective than neoarsphenamine, which has been the drug of choice in the tropical countries which he visited. He noted experimentally that a single dose of penicillin and aluminum monostearate was an effective prophylactic against a chancroid "take" if the interval between the penicillin injection and the inoculation with chancroidal material was zero to four days. Antimony, bismuth, and neoarsphenamine were ineffective prophylactics against experimental chancroid, whereas sulfonamides, streptomycin, aureomycin, penicillin, and chloramphenicol were effective. To test this experimental work, 80 patients with early syphilis in Southern Rhodesia were given one injection of 2,400,000 units of procaine penicillin with 2% aluminum monostearate. Of these "many must have had a double infection with soft sore," for in a previous similar group of 75 patients with multiple penile lesions, all of them were proved to have chancroid and 65 had primary syphilis also. Of the 80 patients treated, only 12 required additional therapy with sulfadiazine or mild mercurous chloride (calomel) ointment to cause healing of all the lesions. Four patients with lymphogranuloma venereum were treated with the same dose of penicillin with aluminum monostearate and all "were discharged from the hospital in an average of 7 days." Willcox concludes:

> The results of these tests are encouraging and indicate that as soon as the single-shot treatment has been definitely proved to be reasonably effective for early syphilis, it will be medically sound to administer it for all forms of penile sore in African and other such populations, with the proviso that sulfonamide drugs be held in readiness for the few resistant cases of chancroid and for lymphogranuloma venereum. The residue will then consist largely of granuloma inguinale.

Syphilis in the United States and Its Possessions.—Drolet [346] analyzed the registration of syphilis and gonorrhea for New York City for the period 1945 to 1949. Between 1945 and 1949 the cases of syphilis reported declined from 22,690 to 20,489, a decrease of about 12%. Cases of primary and secondary syphilis in New York City have declined from 5,164 in 1945 to 2,218 in 1949. In 1945 they comprised 23% of the total, but in 1949 they were reduced to 11%. Late or latent cases of syphilis now form an increasing proportion of reported cases, two-thirds of the total in 1949. New syphilis cases are found mostly among younger women, but among male patients a substantial proportion is in older men.

In Mississippi, Gray and co-workers [347] found that the mortality rate (per 100,000 population) due to syphilis was 24.5 in 1938 and 9.9 in 1948. The infant

346. Drolet, G. J.: Syphilis and Gonorrhea, New York City, Am. J. Syph. **35**:138-145 (March) 1951.

347. Gray, A. L.; Usilton, L. J., and Iskrant, A. P.: Measurement of Trend of Syphilis in Mississippi, J. Ven. Dis. Inform. **31**:225-230 (Sept.) 1950.

mortality (per 1,000 live births) due to syphilis was 1.2 in 1938 and 0.3 in 1948. But the first admissions to state hospitals with psychoses due to syphilis (per 100,000 population) increased from 3.6 in 1938 to 4.6 in 1948. A study of the number of reported cases of primary, secondary, and early latent syphilis from clinics and institutions shows that the trend of the incidence of syphilis is downward from the first quarter of 1947 and is now approximately the same as in 1942. To evaluate the prevalence of syphilis in Mississippi, a study was done of the percentage of positive reactions to blood serologic tests for syphilis in nonwhite pregnant women on their first admission to an antepartum clinic. In 1938, of 785 women tested, 21.0% had a positive reaction on blood test, while in 1948, of 1,000 women tested, only 10.9% had a positive reaction. Also, in 1938, 21.8% of those examined needed treatment, while in 1948, only 5.6% needed treatment. It is concluded that "the trend of prevalence of syphilis in young nonwhite women in Mississippi has been downward since 1946 and is only approximately half what it was in 1938."

The records of the five Navaho Agency Hospitals from 1944 to 1949 revealed, according to McCammon and his co-workers,[348] a variation of 25.4 to 42.6 cases of syphilis per 1,000 hospital admissions, the prevalence per 1,000 population being roughly one-tenth the incidence of hospital admissions. Three thousand six hundred eighteen children, whose ages varied from 5 to 20 years, received blood tests. Of 3,586 satisfactory examinations there were 23 positive specimens, an incidence of 6.4 per thousand. The laboratory records of the Navaho Medical Center from July 1, 1949, to June 30, 1950, show that 11.9% of the patients tested had positive serologic reactions for syphilis. In the same period, 7.86% of pregnant women had positive blood serologic reactions for syphilis. From these figures it is felt that the prevalence of syphilis for the whole Navaho population is probably less than 5%. Thus, syphilis among the Navahos is not considered a major public health problem.

In the summer of 1949, Warner and his co-workers [349] made a census of adults living in Studytown, Ga., and from the material gathered a study was made of the social class structure of the community. In November a community-wide mass blood-testing and chest roentgenogram program was conducted. The results of the blood tests and subsequent diagnostic procedures were compared with the data secured from the earlier social study. In the white population only 12 positive blood-test results were obtained among the 1,977 persons tested. Sixty-four per cent of the white population was tested. Eighty per cent of the Negro population responded to the initial blood-testing campaign, and through letters and visits blood tests were secured on the remainder. Of the Negro men, 13.8% showed a positive or doubtful result to the blood test. Of the women, 13.4% showed a positive or doubtful result. Higher percentages of positive and doubtful results were found in the lower social classes. This finding was more pronounced among the women than among the men. The prevalence rate of positive and doubtful test results found in the initial campaign was 13.1%, and the prevalence rate found in the total population was 13.6%. Comparison of the percentage rates of previously unknown cases of syphilis on the first and on the second surveys showed that the rates for both men and women were higher in the second survey. The difference for women

348. McCammon, C. J.; Dufner, F. J., and Felsman, F. W.: Syphilis Among the Navaho Indians, J. Ven. Dis. Inform. **32**:28-33 (Feb.) 1951.

349. Warner, W. L.; Hill, M. C.; Bowdoin, C. D.; Rion, J. W., and McCall, B.: Syphilis Prevalence and Community Structure, J. Ven. Dis. Inform. **32**:157-166 (June) 1951.

was considerably higher than that for men. The respective rates for the first and second surveys are 4.0 and 5.3 for men and 3.7 and 11.8 for women. In the Negro population two-thirds of those with positive or doubtful test reactions had previously been treated for their infection. This fraction was larger for the men than for the women. Among the men with positive reactions on blood tests, there was a slight indication of a direct relationship between social class and the percentage with previous treatment for syphilis. Among the women, this relationship was an inverse one.

Dr. Jack C. Haldeman [350] reported on general health problems in Alaska. The incidence of syphilis is lower in Alaska than was previously thought. Serologic surveys conducted in some villages failed to disclose a single person infected with syphilis. Morbidity reports of the Alaska Department of Health indicated that once syphilis is introduced into a village, it frequently assumes epidemic proportion. A Canadian study which may be read in conjunction with this article is the report by Orr and Rentiers [351] of their results in attempting to control syphilis in northern Alberta, the territory contiguous to the Alaska Highway.

Alcohol and Venereal Disease.—Tottie [352] reports on the results of the investigations of the Temperance Committee of 1944 to determine the influence of alcohol on venereal disease. Although 14,000 records were analyzed and certain interesting data collected, the investigation seems to provide no clear indication of how much greater the risk of contracting a venereal disease is for a person under the influence of alcohol than for the total abstainer.

Examination and Certification of Prostitutes.—The editors of *The Journal of the American Medical Association* [353] recall that on two occasions the American Medical Association has declared its position with regard to the medical examination and certification of prostitutes. In 1942 the Association's House of Delegates passed and in 1945 the House reaffirmed the following statement [354]:

> *Resolved,* That the House of Delegates of the American Medical Association takes the following stand: (1) that the control of venereal disease requires elimination of commercialized prostitution, (2) that medical inspection of prostitutes is untrustworthy and inefficient, gives a false sense of security and fails to prevent the spread of infection, and (3) that prostitution is unlawful, and physicians who knowingly examine prostitutes for the purpose of providing them with medical certificates to be used in soliciting are participating in an illegal activity and are violating the principles of accepted professional ethics.

The American Social Hygiene Association, as a result of field studies made during the past two years, has reported to the American Medical Association that, while great progress has been made, there is a small number of physicians in the few cities still tolerating commercialized prostitution who continue periodically to examine prostitutes and provide them with certificates for use in soliciting trade. With military and industrial mobilization for national defense now in progress, it

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350. Health Problems in Alaska, Miscellany, J. A. M. A. **145**:108 (Jan. 13) 1951.

351. Orr, H., and Rentiers, P. L.: A Study of Syphilis in Northern Alberta, A. M. A. Arch. Dermat. & Syph. **63**:85-90 (Jan.) 1951.

352. Tottie, M.: Alcohol and Venereal Disease, Acta dermat.-venereol. **30**:450-452, 1950.

353. Examination and Certification of Prostitutes, editorial, J. A. M. A. **146**:564 (June 9) 1951.

354. Resolution on Control of Venereal Diseases, New Business, J. A. M. A. **119**:656 (June 20) 1942.

may be desirable to review the reasons that led the American Medical Association to declare such practices unethical. The editors reaffirm the futility of examination and certification of prostitutes. A statement on prostitution by Stokes [355] in 1942 may be mentioned in this connection.

Case Finding.—Numerous articles have been written in the past year on case-finding procedures and results. We are presenting some of these articles in order to illustrate the field covered and are referring only to some of the more general presentations.[356]

Publicity Technique of a Venereal Disease Campaign: The Division of Venereal Disease Control, Department of Public Health, Philadelphia,[357] planned the publicity for its venereal disease campaign from June to November, 1949, so that the advertising would be concentrated in the high-prevalence areas. A single diagnostic center was utilized as being psychologically most effective. Saturation-type approaches to the persons in the high-prevalence areas were attempted with a tabloid newspaper, car-cards, and sound trucks. Also utilized were newspaper stories, newspaper advertisements, a blimp with 27-ft. illuminated letters spelling "V. D. Campaign," radio stories, juke-box records, leaflets, and pamphlets. These techniques were thought to be especially useful in the high-prevalence areas which are the areas of greatest population density. They were designed to appeal to nonwhite persons having a poor economic and educational status.

Venereal Disease Exhibit at County Fairs: The 1950 version of the venereal disease tent show presented at Michigan fairs during August and September attracted 155,585 persons.[358] As the entire project cost the Michigan Department of Health $11,628, the per person cost was 7.5 cents. There was a 448% increase in attendance in 1950 over 1949. The showing of movies was not utilized, but instead there was a "walk-through type of medical exhibit with a front that would appeal to thirst for sex information." There were separate sections for men and women, each section containing eleven fluorescent-lighted panels. On each panel were posters illustrating the course of syphilis and gonorrhea. Only a single publication was given away. At five of the eight fairs free blood tests were offered, but few persons availed themselves of this opportunity.

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355. Stokes, J. H.: A Statement on Prostitution in Venereal Disease Control, J. Ven. Dis. Inform. **23**:195-198 (May) 1942.

356. Wright, J. J., and Sheps, C. G.: Role of Case Finding in Syphilis Control Today, Am. J. Pub. Health **40**:844-849 (July) 1950. Case Finding Around the Country: The Hunting of the Spirochete, J. Social Hyg. **36**:291-304 (Oct.) 1950. Lancaster, W. B., and Foote, F. M.: The Battle Against Blindness, J. A. M. A. **145**:26-30 (Jan. 6) 1951. Koch, R. A.: Penicillin Is Not Enough: Social and Educational Factors in the Prevention of Venereal Disease, and How San Francisco Deals with VD and Sexual Promiscuity in a Community Program Based on Education for Family Life, J. Social Hyg. **36**:305-316 (Oct.) 1950. Vaughn, C. L., and Freiberg, A. D.: A Pilot Study of the Navy's Educational Program on Venereal Disease: I. Sailors' Opinions About the Effectiveness of the Program, Am. J. Syph. **34**:476-480 (Sept.) 1950; II. Some Attitudes and Practices Which Hinder Effective Control by Educational Measures, ibid. **34**:481-485 (Sept.) 1950; III. Suggestions for Improving the Program, ibid. **34**:486-489 (Sept.) 1950.

357. Gumpert, G.; Ingraham, N. R., Jr., and Burke, M. J.: Venereal Disease Case Finding in High-Prevalence Areas: I. Procedures Used, J. Ven. Dis. Inform. **32**:60-69 (March) 1951.

358. Cowan, J. A.: A New Approach to Venereal Disease Education at Michigan Fairs, J. Ven. Dis. Inform. **32**:91-94 (April) 1951.

Freeble and his colleagues,[359] of the Division of Communicable Diseases of the Ohio Department of Health, describe their 1949 county fair program. They give complete details for planning and setting up a tent in which panels are displayed, literature distributed, and films projected.

Investigation into Technique of Mass Education, and an Attempt to Find the Difference Between Volunteers for Treatment and Nonvolunteers: Morse and Iskrant [360] aimed (*a*) to attempt to describe some of the problems of study of venereal disease education; (*b*) to outline a broad program of research into these problems; (*c*) to present briefly the results of a preliminary study following this research plan. The study of 1,098 patients with primary and secondary syphilis was done by interviews reported on questionnaires. As many facts as possible were secured to attempt to explain why some patients were volunteers and others nonvolunteers.

Influence of Venereal Disease Education on Clinic Attendance and Sexual Promiscuity: To evaluate the most productive type of venereal disease education, 90 patients attending the venereal disease clinic at Victoria Hospital, London, Ontario, Canada, were each given two interviews by Buck and Hobbs.[361] At the first interview a general social history was taken, and at the second there was a discussion of the patient's infection and his experience with venereal disease education. It was found that previous education had no influence upon sexual behavior, but it was helpful in bringing the patient to the clinic voluntarily when infection was suspected. The patients in this study fell into two groups. One group, heavy drinkers with minimal education, believed that venereal disease education served only as a method for bringing persons into clinics for treatment. The other group, of higher educational level and from more stable homes, believed that education could prevent promiscuity and diminish the incidence of venereal disease.

Syphilitics Interviewed to Determine Why Some Volunteered for Treatment and Others Did Not: Five hundred Mississippi Negroes with infectious syphilis were interviewed exhaustively by Gray's group [362] to determine why some volunteered for treatment and others did not. Information was secured from them on the nature and duration of their venereal disease symptoms, their knowledge of syphilis, their family and community interests, and their emotional and vocational orientations. Persons with venereal disease symptoms most frequently consulted the Negro mother; so her aid must be enlisted in spreading correct information. Both men and women received the poorest advice about their venereal disease symptoms from their own spouses. The outstanding characteristic of nonvolunteers was apathy toward their infection. They are geographically and psychologically isolated persons with a fatalistic attitude toward all diseases. In the Mississippi study the ratio of volunteers to nonvolunteers was about 2 to 1. But almost half of all the volunteers had waited until after the appearance of a second symptom of

359. Freeble, C. R., Jr.; Wright, E. O.; Donohue, J. F., and Pratt, A. D.: Suggested Technics for Mass Health Education at County Fairs, J. Ven. Dis. Inform. **31**:308-314 (Dec.) 1950.

360. Morse, J. W., and Iskrant, A. P.: Syphilis Case Finding Through Education, J. Ven. Dis. Inform. **32**:150-157 (June) 1951.

361. Buck, C. W., and Hobbs, G. E.: The Patient's Attitude Toward Venereal Disease Education, J. Ven. Dis. Inform. **31**:204-208 (Aug.) 1950.

362. Gray, A. L.; Bauer, T. J.; Usilton, L. J., and Carlson, R. O.: Case Finding Through an Understanding of Known Syphilitic Patients, J. Ven. Dis. Inform. **32**:144-149 (June) 1951.

venereal disease before seeking diagnostic help. The factor which appeared most closely related to fast or slow volunteering was the degree of personal concern which an individual person felt about his venereal disease symptoms. Twenty-six per cent of those interviewed had reinfections. These persons may seek escape from personal, family, and job problems by sexual promiscuity. It is concluded that concern over the damage and discomfort which venereal diseases may cause, the level of information which respondents have about these diseases, and the prior experiences of respondents in solving their own personal problems, all played significant roles in determining which persons volunteered for diagnosis of their infections and which of them did not.

Testing Programs: The "multiphasic" diagnostic screening unit (including test for syphilis) established as a primary public health diagnostic function is condemned by Smillie [363] as "unsound in its concept, untenable in its principles and indefensible in its logic."

Fiumara and his co-workers [364] report that as of Dec. 1, 1950, Massachusetts has agreed to honor the marriage certificate forms of 34 states, 2 territories, and 1 Canadian province. In return, 16 of the 39 states and the Territory of Hawaii have agreed to honor the Massachusetts Premarital Examination Certificate form when properly completed.

Freeble's group [365] performed blood tests for syphilis in 1949 on 7,508 members of the Ohio National Guard, the total membership of which is about 12,000. Of these, 61 tests gave positive reactions. This is a syphilis rate (per 1,000 persons tested) of 8.1. It is much lower than the rate of 25.8 among selectees and volunteers in Ohio examined in 1940 and 1941. This lower rate might be due to a decrease in syphilis among young men in Ohio from 1941 to 1949, to the fact that the men of the National Guard are a select group with higher ideals and morals, or to the fact that the Guardsmen who were not tested because of absenteeism may represent men who failed to volunteer for the blood test because they feared detection of syphilis.

Contact Investigation of Private Patients with Syphilis: In January, 1944, the Illinois State Department of Public Health introduced the assignment and report form to tabulate and analyze the several types of contact investigation. Sklar and Schuman [366] evaluate the results from 1944 through 1949 in interviewing the patients of private physicians and in tracing their contacts. When a report of a case of primary, secondary, or early latent syphilis or gonorrhea is received, permission of the physician is asked to interview the patient. Of the 6,588 cases reported, 5,914, or 89.8% of the patients, were permitted to be interviewed. These patients named 5,368 contacts, of whom 2,462 were examined, representing 41.6

363. Smillie, W. G.: "Multiphasic" Screening Tests, J. A. M. A. **145**:1254-1256 (April 21) 1951.

364. Fiumara, N. J.: Massachusetts Premarital-Examination Law and Interstate Marriages, New England J. Med. **244**:194-196 (Feb. 1) 1951. Fiumara, N. J.; Colby, E. W.; Talbot, H. P.; Lade, J. H.; McAteer, R. F.; Aiken, R. B., and Jones, R. P.: A Plan to Simplify Premarital Laws, Am. J. Pub. Health **40**:1238-1240 (Oct.) 1950.

365. Freeble, C. R., Jr.; Wright, E. O.; Donohue, J. F., and Bolin, J. B.: The Ohio National Guard Blood-Testing Program, J. Ven. Dis. Inform. **31**:231-234 (Sept.) 1950.

366. Sklar, B. H., and Schuman, M.: Special Contact Investigation of the Patients of Private Physicians, J. Ven. Dis. Inform. **31**:286-290 (Nov.) 1950.

contacts examined per 100 patients interviewed. The proportion of contacts examined to patients interviewed increased from 29.8 in 1944 to 61.0 in 1949. In the six-year period, 1,404 infected contacts were interviewed. Over half (57.0%) of the contacts examined were found to be infected. By this contact investigation of the patients of private physicians, 510 new patients with primary or secondary syphilis were found.

Diagnosis of Congenital Syphilis by Dental Examination: Two thousand one hundred fifty-six children were examined by Bertram [367] for evidence of Hutchinson's teeth. These abnormal teeth were found in 69 children (3.2%). Fifty-three of these were given a blood test for syphilis, and the results on 13 (24.5%) were positive. The occurrence of Hutchinson's teeth was proportionately higher in the older children (13 to 18 years of age) than in the younger children (6 to 12 years old). Assuming that the 12-year-old children were born during 1936, the year in which the intensive venereal disease control program started, the smaller proportion of Hutchinson's teeth found in the younger group presumably reflects the effectiveness of the control program.

Case Finding of Early Syphilis by the Public Health Nurse: During 1949 a survey was conducted by the Wake County Health Department in Raleigh, N. C.,[368] to determine the role of the public health nurse in venereal disease contact investigation. It was concluded that the public health nurse in a generalized public health nursing program has potentialities for syphilis case finding. During 1949, 254 contacts were referred to the nursing service. Of these, 209 were examined, and 61 new cases brought under treatment. From 59 patients with early syphilis interviewed at the health department, 179 contacts were obtained. Among these contacts, 51 patients with early syphilis were found. It was noted that in the development of effective case-finding procedures the interpretative interview should be given primary consideration. The contact investigation integrated well with the public health nurse's other activities.

Case Holding: The Male Defaulter.—Horne [369] presents a study of the "contemporary" male defaulter. Modern methods of treatment and the more "enlightened" attitude of the public to venereal diseases seem to have modified the default pattern and its significance. The material of the study was taken principally from the records of the male venereal disease clinics at Edinburgh, Scotland, from January, 1948, to March, 1950. During this period both the medical and the nursing staffs and the schedules of treatment have remained constant. No change in criteria of default was made. As a result of the findings in this study, the author believes that the evidence justifies the modern tendency to emphasize "case finding" rather than "case holding." The successful handling of all the problems associated with default depends to a great extent on the personality, and especially on the patience, of the members of the medical and social-work staff.

A Proposal for Joint Action Against Congenital Syphilis.—Despite the availability of penicillin for the control of syphilis, it is estimated that in this country

367. Bertram, F. P.: The Dentist's Role in Finding Congenital Syphilis, J. Ven. Dis. Inform. **31**:191-193 (July) 1950.

368. Sulla, A. C.; Wakefield, F., and Hunt, M. E.: Case Finding of Early Syphilis by the Public Health Nurse, J. Ven. Dis. Inform. **32**:122-129 (May) 1951.

369. Horne, G. O.: The Contemporary Male Defaulter, Brit. J. Ven. Dis. **26**:164-171 (Dec.) 1950.

there are 100,000 children 10 years of age or less with undiscovered congenital syphilis. Although penicillin has been utilized during the past four years, about a third of the 14,000 cases of congenital syphilis reported each year are of children 4 years old or younger. To correct this situation, Huse and Aufranc [370] make five recommendations and plead for mutual assistance and action. They suggest that serologic tests for syphilis be done not only early in pregnancy, but also in the third trimester. Since an untreated pregnant woman with syphilis is a medical emergency, treatment should be started immediately in the hope of offering some protection to the baby. All babies born of syphilitic mothers should have the new filter paper microscopic test. If the test gives a positive result, and if the doctor is not sure a four-month follow-up observation is possible, "protective penicillin therapy" should be given. Successful control of congenital syphilis requires the cooperation of all those interested in child health. This includes the representatives of the Children's Bureau, United States Public Health Service, state medical societies, local health departments, private practitioners, and midwives. Widespread educational campaigns are urged and mass testing with the filter paper microscopic test in areas where the incidence of syphilis in children is as high as 2 to 4%.

370. Huse, B., and Aufranc, W. H.: A Proposal for Joint Action Against Congenital Syphilis, J. Ven. Dis. Inform. **31**:174-177 (July) 1950.

News and Comment

ANNOUNCEMENTS

Graduate Instructional Course in Allergy.—On April 4, 5, and 6, 1952, at Pittsburgh, The American College of Allergists will offer an instruction course in allergy. To insure complete coverage, the College has called in some 60 well-known authorities in the field to give addresses, clinical talks, and demonstrations. The program has been designed for physicians in other fields of practice, especially those in general practice, that they may learn to recognize and manage the allergic component in the complaints of their patients. For further information and a copy of the program, write to The American College of Allergists, LaSalle Medical Building, Minneapolis 2.

Symposium on "The Effect of ACTH and Cortisone upon Infection and Resistance."—Dr. Gregory Shwartzman, Chairman of the Section on Microbiology of the New York Academy of Medicine, announced that a symposium on "The Effect of ACTH and Cortisone upon Infection and Resistance" will take place on Thursday and Friday, March 27 and 28, 1952, at the New York Academy of Medicine. Contributors to the symposium will be Dr. F. L. Engel (metabolism); Dr. W. W. Umbreit (enzymatic reactions in rat tissues); Dr. W. E. Ehrich (lymphoid tissue); Dr. C. A. Ragan Jr. (loose connective tissue); Dr. E. E. Fischel (antigen-antibody reactions); Dr. H. C. Stoerk (resistance to infections and tumor grafting); Dr. A. McGehee Harvey (bronchial asthma and drug idiosyncrasy); Dr. L. Thomas (toxins and experimental Streptococcus hemolyticus); Dr. A. Wolf (spontaneous trypanosomiasis); Dr. G. Shwartzman (experimental poliomyelitis); Dr. M. Finland (bacterial infections and malaria); Dr. M. B. Lurie (tuberculosis); Dr. A. C. Woods (infections of the eye); Dr. T. B. Turner (experimental syphilis). The meetings will be held in the Academy building, 2 E. 103 St., New York, and will be open to all who are interested.

Seminars on "Modern Concepts in Psychiatry."—The following seminars on Modern Concepts in Psychiatry will be given during March and April, 1952, at the Veterans Administration Hospital, Downey, Ill., or the Veterans Administration Regional Office, 366 W. Adams St., Chicago: March 18, 10 a. m., "The Acute Psychoses" (Downey); 1 p. m., "Discussion of a Case Presentation" (Downey); 8 p. m., "The Case of the Mental Patient in Hospital and After Release" (Chicago); March 26, 10 a. m., "The Pseudoneurotic Form of Schizophrenia" (Downey); 1 p. m., "Discussion of a Case Presentation" (Downey); 8 p. m., "Some Theoretical and Clinical Aspects of Anxiety" (Chicago); April 2, 10 a. m., "Functional Organization of the Brain" (Downey); 1 p. m., "Discussion of a Case Presentation" (Downey); 8 p. m., "Experimental Epilepsy" (Chicago); April 8, 8 p. m., "Schizophrenia and Schizophreniform States" (Chicago); April 30, 10 a. m., "Changes in Dart Test Performance Brought About by Prefrontal Leucotomy" (Downey); 1 p. m., "Discussion of a Case Presentation" (Downey); 8 p. m., "Clinical and Interpretive Aspects of Some Manifestations of Depression" (Chicago).

***Diabetes*, New Journal of the American Diabetes Association.**—*Diabetes*, the journal of the American Diabetes Association, will appear bimonthly beginning with the January-February, 1952, issue. It will be devoted to clinical and research reports on diabetes and related aspects of medicine and will be the Association's official scientific and organizational publication, replacing its annual *Proceedings* and its quarterly *Diabetes Abstracts*, both of which have been published for the past 10 years. *Diabetes* will be edited by Frank N. Allan, M.D., of the Lahey Clinic, Boston, First Vice-President of the American Diabetes Association. Dr. Allan will be advised and assisted by a distinguished Editorial Board under the chairmanship of Charles H. Best, M.D., of the University of Toronto, Toronto, Canada, co-discoverer, with the late Sir Frederick Banting, of insulin and its use in the control of diabetes. Correspondence concerning both editorial and business matters should be addressed to the Editorial Offices, *Diabetes*, American Diabetes Association, Inc., 11 West 42d St., New York 18.

Eighth Annual Meeting of the American College of Allergists.—The eighth annual meeting of The American College of Allergists will be held at the William Penn Hotel, Pittsburgh, on April 7, 8, and 9, 1952. The College is offering an unusually practical program for its fellows, members, and guests.

In addition to 20 addresses on general topics and special scientific investigations, there will be round tables at luncheons and sectional meetings devoted exclusively to the psychosomatic aspects of the allergic patient, allergy in infants and children, and allergic manifestations in the skin, as well as those seen in the eye, ear, nose, and throat.

An innovation for meetings of the allergists will be a session devoted to the problems of the allergic patient as met in modern industrial medicine. All reputable physicians are welcome to attend. For more particulars, write the College, LaSalle Medical Building, Minneapolis 2.

Examination for Fellowship in American College of Chest Physicians.—The Board of Examiners of the American College of Chest Physicians announces that the next oral and written examinations for Fellowship will be held in Chicago on June 5, 1952. Candidates for Fellowship in the College who wish to take the examinations should address their requests to the Executive Secretary, American College of Chest Physicians, 112 E. Chestnut St., Chicago 11.

Grants for Research on Human Fertility.—The Planned Parenthood Federation of America is offering grants for basic research relating to problems of human fertility, including infertility and conception. The research grants are being made available through the Federation's Robert L. Dickinson Research Memorial. Applications will be received and screened by a subcommittee of the Medical Committee of the Planned Parenthood Federation. Projects recommended by the full Medical Committee will be considered by the Federation's Executive Committee for allocation of funds.

Prospective applicants should address the Robert L. Dickinson Research Memorial, Planned Parenthood Federation of America, 501 Madison Ave., New York 22.

Meeting of American College of Chest Physicians.—The Eighteenth Annual Meeting of the American College of Chest Physicians will be held at the Congress Hotel, Chicago, June 5 through 8, 1952. A scientific program covering all recent developments in the treatment of heart and lung disease is being arranged.

Postgraduate Course in Diseases of Chest.—The Fifth Annual Postgraduate Course in Diseases of the Chest, sponsored by the Council on Postgraduate Medical Education and the Pennsylvania Chapter of the American College of Chest Physicians and the Laennec Society of Philadelphia, will be presented at the Warwick Hotel, Philadelphia, March 24 to 28, 1952. A program covering the entire field of heart and lung disease is being arranged. Dr. Chevalier L. Jackson, Philadelphia, President of the American College of Chest Physicians, is chairman of the postgraduate course committee. Physicians interested in attending the postgraduate course are invited to communicate with the Executive Offices, American College of Chest Physicians, 112 E. Chestnut St., Chicago 11.

United States Air Force Offers Commissions.—The United States Air Force has announced a program whereby commissions will be offered to young men and women practicing in all fields of medicine and in all allied specialized vocations.

The list of vocations includes doctors of preventive medicine, gastroenterologists, obstetricians, gynecologists, allergists, anesthesiologists, ophthalmologists, otorhinolaryngologists, neurologists, internists, general and orthopedic surgeons, radiologists, oral surgeons, periodontists, prosthodontists, medical supply and medical equipment maintenance specialists, sanitary engineers, clinical laboratory technicians, general-duty and anesthetist nurses, dietitians, and physical therapists.

Each classification has a different set of requirements for each grade from second lieutenant through the higher grades. The First Air Force has set up clerical facilities for promptly answering all queries concerning these commissions. Inquiries should be directed to the Air Surgeon, Headquarters, First Air Force, Mitchell Air Force Base, New York.

Symposium on Hepatitis.—The Fourth Conference of the International Society for Geographic Pathology will be held in Liége, Belgium, July 15 to 18, 1952. The subject of the symposium is "Hepatitis," but one session of the Conference will be devoted to presentation of papers on other topics. The Conference will cover medical, surgical, physiological, and pathological aspects of hepatitis. For information write to Dr. William B. Wartman, Secretary, National Committee for the United States, International Society for Geographic Pathology, Northwestern University Medical School, 303 E. Chicago Ave., Chicago 11.

GENERAL NEWS

Pharmacologists Recommend That Heroin No Longer Be Used.—The World Health Organization's Expert Committee on Drugs Liable to Produce Addiction has recommended that diacetylmorphine (heroin) no longer be used for medical purposes, and that it be replaced in all countries with other, less dangerous drugs. The Committee also has recommended that thirteen drugs belonging to the meperidine, methadone, and morphinan types be placed under international control, through machinery provided by the United Nations under various international conventions. The recommendation on diacetylmorphine was made after the Committee learned that, on the World Health Organization's request, 50 countries have already discontinued or are willing to discontinue the medical use of the drug. As recently as 1949, available data indicated that only 24 countries had taken this step.

Book Reviews

Industrial Health and Medical Programs, Statements, Tables, and Charts. Selected and compiled by Margaret C. Klem, Margaret F. McKiever, and Walter J. Lear, M.D. Price, $1. Pp. 397, Industrial Hygiene Division Publication No. 15, Public Health Service, Federal Security Agency, 1951.

A composite of publications in the field of industrial health collected by the authors and edited by them is presented in this volume. The text consists of direct quotations and charts from the original articles, uniquely arranged to give continuity to the material. The volume is divided into eight sections dealing with various phases of industrial medicine and contains a wealth of material both as text and as statistical charts. Section II develops the chronological recognition of the need for medical programs in industry. Other sections concern the organization, personnel, and costs of plant or industrial medical programs for both small and large groups. Charts are included indicating the seasonal incidence of disease in industry, age factors in absenteeism, and numerous other details. Floor plans and equipment for industrial health units are suggested.

While limited in its scope in terms of the needs of the practicing physician, this volume is a mine of information for industrial physicians, industrialists, medical economists, and those interested in the teaching of preventive medicine. It will serve as a valuable reference book to anyone interested in the subject material.

The Integration of Psychiatry and Medicine: An Orientation for Physicians. By William B. Terhune, M.D. Price, $2.75. Pp. 177. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1951.

Terhune's material is presented in an interesting fashion, emphasizing the usual psychiatric problems facing the physician and offering practical suggestions for dealing with them. The subject matter is aimed at interns, residents, and physicians outside the field of psychiatry. The writer has treated of a large and difficult field at a level consistent with the training and experience of the young physician. Eight lectures and demonstrations make up a volume of 169 pages. Those who have not had training in psychiatry will find this book interesting and valuable. Teachers of psychosomatic medicine might find it useful in orienting the student and as a proved method of interesting physicians in mental hygiene and psychiatry.

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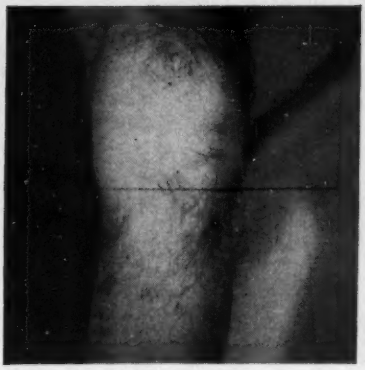

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Ward, L. E., Slocumb, C. H., Polley, H. F., Lowman, E. W., and Hench, P. S.: *Proc. Staff Mtgs., Mayo Clinic* **26**: 361, September 26, 1951.

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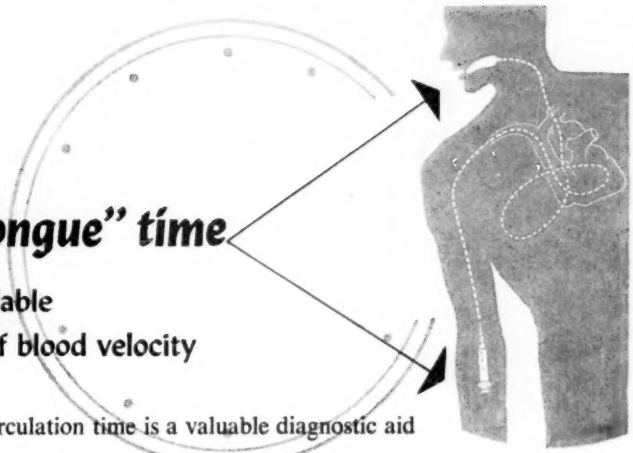

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1. From Burton Stevenson's "Home Book of Proverbs, Maxims and Familiar Phrases." Macmillan Co., 1948, p. 2028.
2. Heller, E. M.: The Treatment of Essential Hypertension. *Canad. Med. Assn. Jour.*, 61:293-299, Sept., 1949.

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